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Experiences with Radioactive Phosphorus in Tumor Detection
Edwin B. Dunphy, Joseph L. Dowling Jr., and Alfred Scott

Ocular Involvement in Chondrodystrophia Calcificans Congenita Punctata
Mansour F. Armaly

Vogt-Koyanagi-Harada Disease
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Retinitis Pigmentosa with Normal Electroretinogram
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The Protein Components of Human Tears
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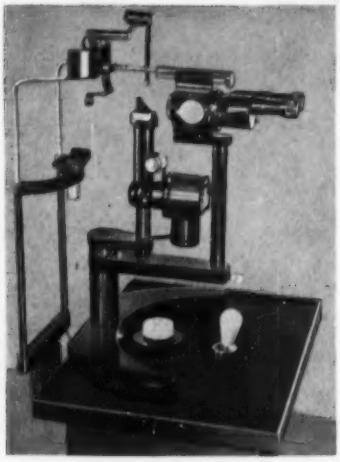

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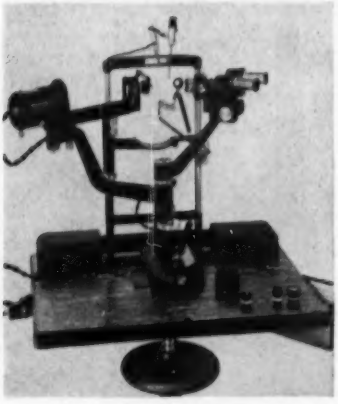

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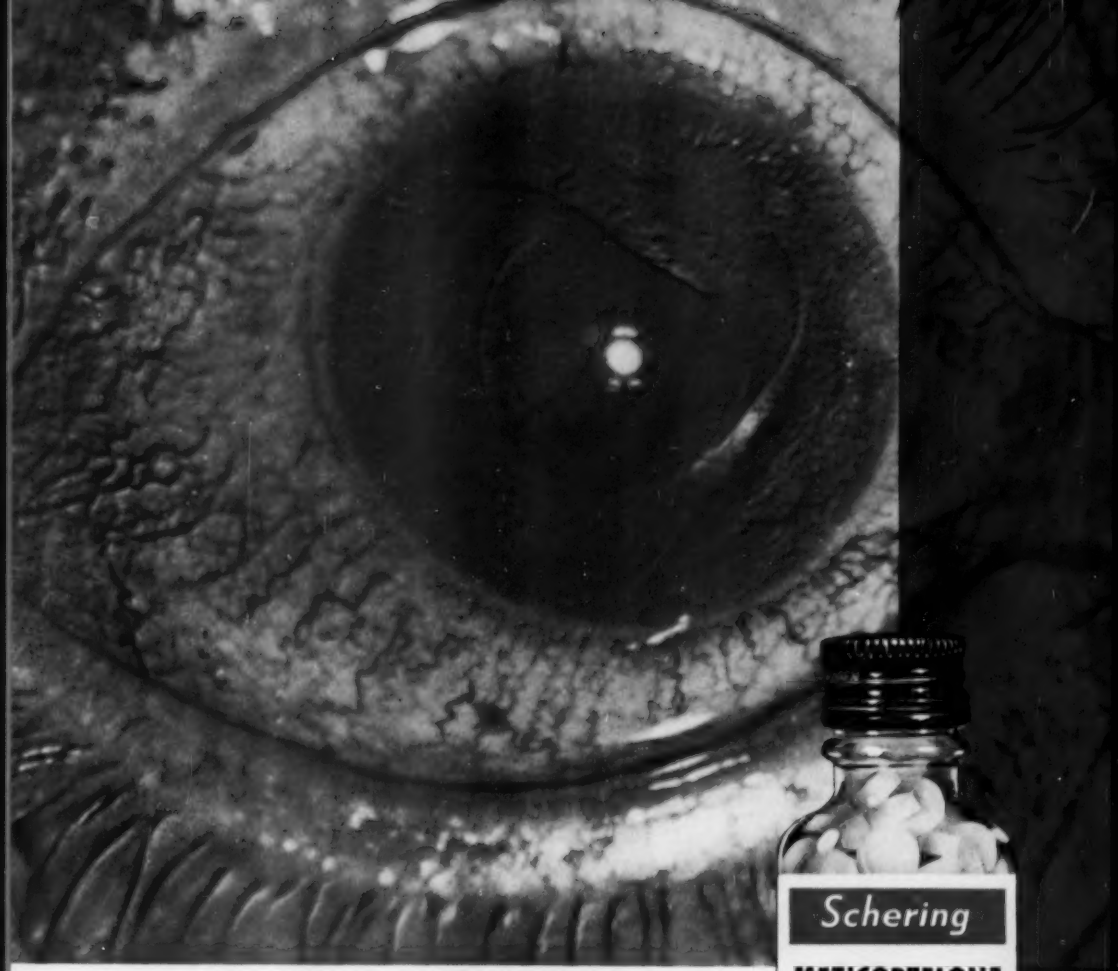

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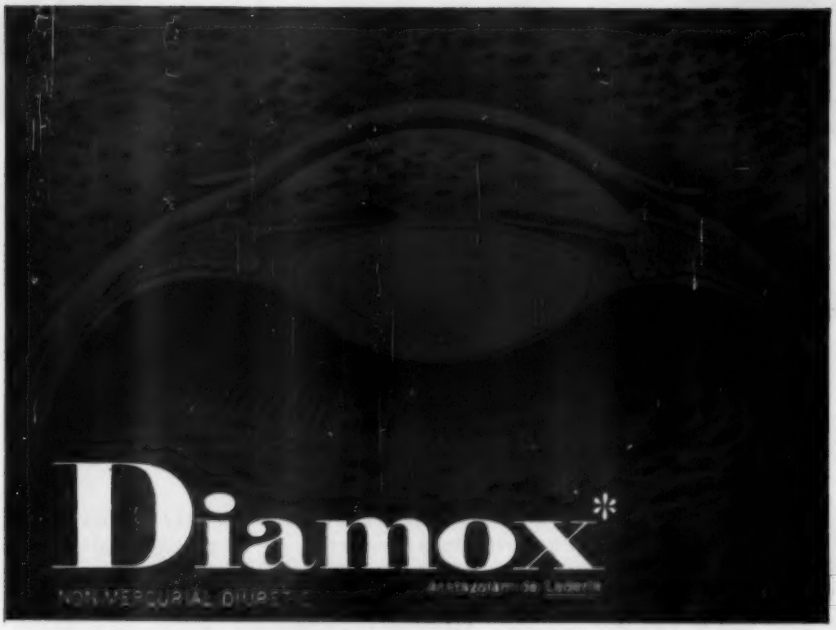

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Experience with Radioactive Phosphorus in Tumor Detection

EDWIN B. DUNPHY, M.D.; JOSEPH L. DOWLING Jr., M.D., and ALFRED SCOTT, M.D., Boston

The importance of correctly diagnosing intraocular tumors need not be emphasized. Yet a recent review of 862 eyes submitted to a large pathology department as clinically malignant revealed that 102, or 12%, were found to contain no malignancy.[1] The use of radioactive phosphorus (P^{32}) to detect malignant ocular tumors has been in vogue at certain ophthalmic centers since 1952. From several papers already published on the subject, it has been definitely shown by radioassay[2] and by radioautographs[3] that malignant tumors concentrate P^{32} to a greater degree than do other ocular tissues after intravenous injection. Other in vitro and in vivo studies[4] have demonstrated that this increased uptake can often be detected by a small Geiger counter if this instrument can be placed on the eyeball sufficiently near the tumor area. Furthermore, it has been shown that this increased concentration does not occur in serous detachments of the retina, vitreous hemorrhage, and degenerative lesions of the fundus.[5,6] Therefore, it seems reasonable to expect that this might prove to be a reliable method to differentiate intraocular tumors from those lesions which might be confused with them in vivo.

Since the original successful application of the P^{32} test by Thomas, Krohmer, and Storaasli,[3] in 1952, several papers have appeared, reporting favorable results for the most part. The largest series of cases has been reported by Terner, Leopold, and Eisenberg[6] in the A. M. A. ARCHIVES OF OPHTHALMOLOGY, January, 1956. This valuable report includes many cases of external malignancy and various other conditions such as cataracts, glaucomas, retinal detachments, etc., but, if one excludes these, there remain 36 cases of proven intraocular malignancy in which P^{32} was employed.

Before the P^{32} test is accepted or rejected by ophthalmologists as a whole, other series of cases must be recorded and evaluated, and it is for this reason that we wish to report some of our experiences at the Massachusetts Eye and Ear Infirmary in a series of 50 cases of intraocular lesions of either proved or suspected malignancy. We have seldom employed the test on extraocular lesions, where biopsy seems to be the most direct way of obtaining a diagnosis. It is in the intraocular lesions, in which biopsy is hazardous, that P^{32} would seem to offer its maximum usefulness.

Our present method of performing the test consists of giving 750μc of P^{32} intra-

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venously as buffered sodium phosphate. This is the highest dose given to an average-sized adult. To small frail adults we give only 500μc. Children under 12 should receive much less. With this dosage, the amount of total body radiation is above that customarily permitted to laboratory workers under daily exposure, but, since almost 20% of the P^{32} given is excreted in the first 24 hours and since its half-life is only 14 days, it is considered safe. Approximately 24 hours later the counting is begun, with the patient in a prone position. Both eyes are anesthetized beforehand with 2 to 3 drops (about 0.12 to 0.18 cc.) of tetracaine (Pontocaine) hydrochloride, 0.5%, and the patient is instructed to look steadily in a direction which will enable the ophthalmologist to place a specially designed Geiger counter as close as possible to the suspected lesion. It is best to have as little moving about in the room as possible so as not to divert the patient's attention. The counter is placed squarely in contact with the eyeball for one minute, and the counts are recorded. A similar count is made on the normal fellow eye in a corresponding position. The process is then repeated for each eye, and an average of at least three counts is obtained for each location. In one-eyed persons a remote quadrant of the same eye is used as the control area. The percentage of P^{32} uptake over the lesion in excess of that over the normal area is calculated. An increase of 30% is the minimum requirement for a positive test, since Eisenberg, Leopold, and Sklaroff [5] have shown that variations up to 28% may occur in comparable areas of normal healthy eyes.

Eisenberg, Terner, and Leopold [7] establish their control area at the limbus of the normal eye, averaging the counts taken at the 12, 3, 6, and 9 o'clock positions. They believe that more uniform counts can be obtained by this method. In many of our cases we have used this method as well as the corresponding point method and find very little difference between them.

Tumors of Choroid and Ciliary Body

Thirty-one cases of choroidal and ciliary body lesions were tested in vivo. Twenty-one of these were proved to be malignant melanomas by pathologic examination (Fig. 1). In 15 of these proved cases the tumors were located in such a position as to be

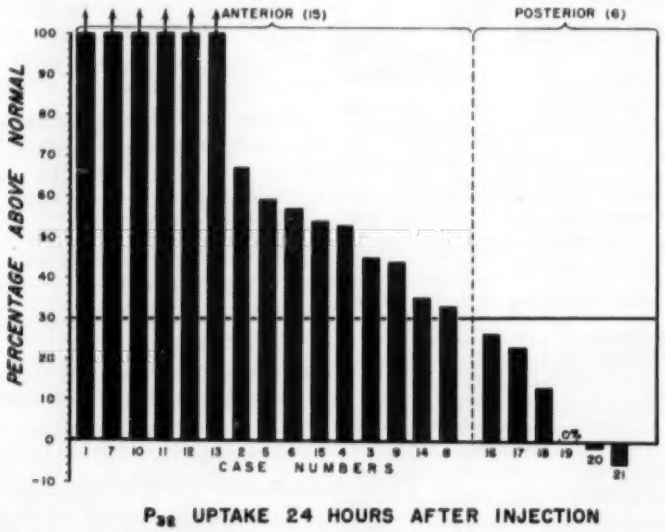

Fig. 1.—P^{32} uptake in 21 proved cases of malignant neoplasms of the choroid and ciliary body.

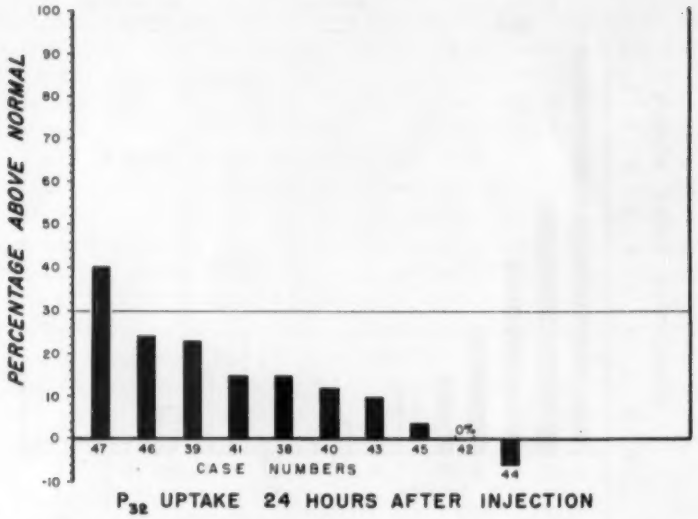

Fig. 2.—P^{32} uptake in 10 cases of presumably benign lesions of the fundus.

accessible to the application of the Geiger counter. In all 15 there was a substantial increase of counts over the tumor area, compared with the same area in the healthy eye. In the six proved cases in which the tumor was located well posteriorly, all showed negative tests.

Ten other eyes with suspicious fundus lesions have been tested, with negative results in nine of them (Fig. 2). Clinically, most of these lesions were considered nonmalignant, and the eyes were not removed. These cases are still under observation. In the one in which the test was positive (Case 47), the clinical diagnosis was disciform degeneration, and subsequent follow-up for two years has confirmed this impression. This was our only false positive test, and no explanation is offered, except to point out that the test, like many other tests in medicine, is not infallible.

Iris Tumors

Sixteen eyes with iris lesions were tested in vivo, a biopsy being performed in ten of them (Fig. 3). In these 10, pathologic examination showed 5 to be malignant melanomas, 3 benign leiomyomas, and the other 2 benign cysts. The test was positive in four of the five eyes containing malignant melanomas, but in one (Case 36) it was negative. The test in Case 36 was clearly a false negative one, showing only 19% increased uptake, whereas examination of the tumor by three pathologists showed it to be malignant melanoma. Again, no explanation is offered except that the tumor was very small and near the pupillary border, which meant that it was about 3 mm. away from the Geiger counter. In the five eyes with benign lesions the test was negative.

In the six eyes in which no biopsy was performed, either because the patient refused surgery or because clinical appearance contraindicated it, the test was negative. These cases are under observation.

Other Lesions

Our experience with retinoblastoma has been very limited, partly because our pediatrics department does not look with favor on small children getting P^{32} at a time when their bone marrow and other blood-forming organs are developing. Another reason is the hazard of a spark from the scaler while

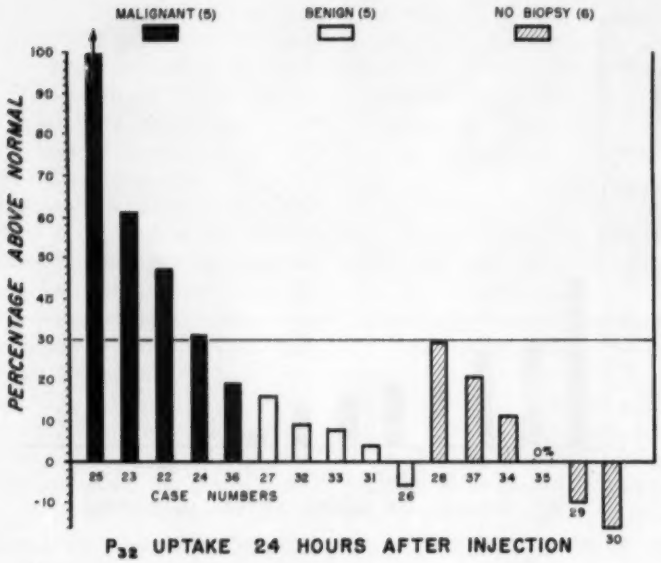

Fig. 3.—P^{32} uptake in 16 cases of iris lesions.

the patient is under ether anesthesia. In the three cases in which we did perform the test prior to enucleation, negative results were obtained in two, although these eyes did contain retinoblastomas and showed positive tests just after enucleation, when the Geiger counter was placed on the sclera directly over the tumor. It is difficult to explain the reason for this, except that the tumors were not very accessible in vivo. Our other case showed a 70% increase in the counting rate before enucleation. The tumor was well forward and, hence, accessible, and differential diagnosis had included melanoma and choroidal hemorrhage because of the dark appearance of the tumor.

Like other investigators, we found that in a number of cases of serous detachment ence in counts between the two eyes. In of the retina there was essentially no differfive of these cases the radioactivity of subretinal fluid obtained during the operation was compared with that of venous blood drawn from an antecubital vein at the same moment (Table 1). In every case, the value was much higher for the blood; the average ratio being 3.59:1. Therefore, on theoretical grounds alone, we would not expect a positive test in serous detachment, and this proved to be the case. Actually, the counts over the detachment tended to be less than those over the normal eyes. An explanation for this might lie in the fact that the detached retina was more remote from the counter and, therefore, contributed less than usual to the total emanations.

Comment

The fact that malignant melanomas concentrate P^{32} in higher amounts than normal ocular tissues is a well-established fact. Therefore, any evaluation of the P^{32} test in detecting intraocular tumors is in reality an evaluation of the methodology em-

Table 1.—*Ratio of P^{32} in Venous Blood to P^{32} in Subretinal Fluid*

Case	Time Interval	Ratio
1	2 hr.	3.1
2	1 hr. 50 min.	4.1
3	3 hr. 15 min.	2.6
4	2 hr. 5 min.	4.85
5	64 hr.	3.3
	Av. ratio	3.59

ployed. Realization of this fact must serve as a strong stimulus to persist in the development of new radioactive techniques, since it is probable that a very high degree of accuracy will some day be obtained. Since the P^{32} uptake is probably a reflection of the level of the phosphorus metabolism of the tumor, this test may ultimately prove to have prognostic implications. Such information might be of significance as regards the utilization of radical surgery or post-enucleation irradiation.

Under present conditions, the P^{32} test seems to provide a high degree of reliability as an adjunct to the clinical diagnosis of choroidal melanomas when they are accessible to the counter by reason of anterior location. Although the maximum range of the β-ray emission of P^{32} is 7 to 8 mm., the average is only 2 to 3 mm. It is, therefore, apparent that negative tests are of no significance in posterior lesions unless the counter can be accurately placed. The P^{32} test would appear to be of considerable accuracy in iris lesions by reason of their accessibility and accurate visualization.

It is obvious that improvement in the technique would greatly enhance the clinical value of the test. Several possible approaches to this end are evident.

It is logical to assume that improvement of the accuracy and value of the test would accrue from incision of the conjunctiva, and possibly detachment of one or two muscles, for direct counting over suspected tumors with localization by transillumination or indirect ophthalmoscopy. This would also obviate the misleading β-ray emanations from other structures, notably the extraocular muscles. The control reading in these circumstances should be reliable by counting over the sclera only 10 mm. or more from the margin of the lesion.

The difficulties inherent with the short-range β-ray emissions might be overcome by the use of radioactive isotopes which emit γ-rays, which have a penetration of several centimeters in tissue. We have attempted to utilize the γ-radiations of potassium 42 and rubidium 86 in a patient with a large choroidal melanoma. This was unsuccessful because of the tremendous background radiation which the counter recorded, which masked that coming from the tumor itself.

Perhaps the most feasible approach is improvement in the shape and flexibility of the counter, which is at present somewhat large and awkward. Bettman and Fellows [8] have devised a curved scintillation counter, and Thomas and Krohmer [9] have recently described a curved Geiger counter with a posterior transilluminator for more accurate localization. We hope that these instruments will soon be available commercially.

Certain other precautions must be kept in mind in using P^{32}. Errors in technique and eccentricities of the counting apparatus can give rise to inaccurate findings. Movement of the patient's eye during the test will naturally throw off the counts. The counter must be applied directly over the sclera, since tipping it or failing to make close application will give a false reading. This has been emphasized by Bettman and Fellows.[10]

Certain other precautions must be kept in mind in using P^{32}. Active inflammatory lesions may give increased counts and, thus, be confused with malignant tumors. Therefore, when possible, these lesions must be excluded by other clinical means. Eisenberg, Terner, and Leopold [7] have shown that, while the uptake of P^{32} by large inflammatory lesions appears similar to that of malignant tumors shortly after the injection, this concentration falls off rapidly in the next few hours, whereas a malignant tumor appears to retain its radioactivity much longer. Hence, they suggest two criteria for differentiating malignancy and inflammation. The affected eye must show at least a 30% higher count than the normal eye 1 hour after injection, and, in addition, there must be an even higher differential count 24 hours later. While all this is undoubtedly true, it seems to us that the inflammatory lesions rarely present a diag-

TABLE 2.—*P^{32} in Malignant Melanoma of Orbital Tissue*

Time After Injection	Counts per Minute		Ratio, Tumor/Normal
	Melanotic Nodule	Normal Tissue	
30 min.	930	405	2.3
1 hr. 45 min.	1,008	359	2.8
22 hr. 45 min.	828	206	4

nostic problem. It is the degenerative and vascular lesions which are more often confused with neoplasms.

Also, we have little confidence in the accuracy of the one-hour reading. The ideal time for obtaining a maximal differential count between normal and abnormal tissue is 24 to 48 hours after injection. This is illustrated by the following case (Table 2): A patient was suffering from an orbital recurrence of an intraocular melanoma following enucleation a year previously. Counts were taken directly over the malignant nodule and over normal orbital tissue several centimeters away at different intervals following P^{32} injection. The test became increasingly positive as time went on. The ratios of normal tissue to tumor tissue were as follows: 30 minutes after injection, 1:2.3; 2 hours after injection, 1:2.8; 23 hours after injection, 1:4. In other words, the tumor tended to retain the P^{32} longer than normal tissue.

Conclusions

In conclusion, it cannot be too strongly emphasized that the use of P^{32} should be regarded as a diagnostic aid and not as a positive diagnostic test. A negative result does not exclude malignancy, whereas a positive result (meaning a 30% or higher differential count 24 hours after injection) is strongly suggestive.

Bearing in mind the limitations already mentioned, we feel that the continued utilization of this isotope will prove to be of increasing value as the present technical difficulties are overcome.

Drs. David Cogan and Taylor Smith examined the pathologic sections, and Dr. William Sweet gave advice; Miss Beverly Whitman gave technical assistance.

243 Charles St. (14).

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Ocular Involvement in Chondrodystrophia Calcificans Congenita Punctata

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Chondrodystrophia fetalis hypoplastica (Conradi,[1] 1914), epiphysial dysplasia puncticularis,[2] calcinosis universalis,[4] epiphyseal dysplasia punctata,[5] chondrodystrophia calcificans congenita,[6] metaphyseal dyscrasia,[7] congenital stippled epiphyses,[8] and chondrodysplasia calcificans congenita punctata are names that were coined at one time or another to designate a congenital syndrome which includes, among other things, a premature generalized deposition of calcium salt in discrete foci in the regions of enchondral ossification in the skeletal framework. However, since Conradi first alerted the medical profession to this syndrome more information has accumulated, which, though still far from clarifying our understanding of this disease, has enabled us to appreciate not only that this syndrome is a chondrodystrophy, although this is one of its prominent manifestations, but also that not all calcified stipplings of the epiphyses belong to this syndrome.

The radiologists were the first to report this condition, because of its characteristic x-ray appearance; later on, the orthopedists and the pediatricians became interested. The ophthalmic literature, till recently,[10] was unaware of this syndrome, which includes, among its important manifestations, bilateral congenital cataracts. I have had the chance to observe, treat, and follow two patients with this condition, and I feel that a review and presentation in the ophthalmic literature is warranted.

Incidence

The incidence in the general population is estimated to be 1 in 500,000.[11] To date, 44 cases of "stippled epiphyses" have been reported in the literature. These, however, include 13 cases in which the only manifestation was the radiologic finding of "stippled epiphyses," not associated with any abnormality in the growth of the bones or the body in general or with any evidence that degeneration had occurred at the epiphyses as judged by the normal size and shape in the x-ray film. Some authors,[9,10] impressed by the presence of stippling in the epiphyses, considered that these otherwise normal persons exhibited a minor form of the disease. However, orthopedists as well as radiologists generally feel that calcium deposition in the epiphyses giving a stippled appearance is encountered frequently in persons with normal skeletal development as well as in a variety of localized bone diseases in the adult,[2,6,18] and they warn against including these cases under this syndrome. Here the congenital calcification is invariably associated with pathologic changes at the epiphyses and retarded skeletal growth and with a variety of extraskeletal manifestations, and the majority of the effected patients die before the age of 2 years. With this specification in mind, the number of cases belonging to this syndrome reported to date would be 31.

Sex Incidence.—The reported cases include more females than males, the ratio being close to 4:3.

Familial Incidence and Hereditary Factor

There is some evidence in the literature that there may be a tendency toward a familial incidence of this disease.[6] Raap[13] reported four cases, a pair of twins and two brothers, in one family. However, the exact role of heredity has not been determined.

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Signs

Although the names cited above are all variations of one theme, emphasizing the skeletal pathology, the syndrome is by no means exclusively a chondrodystrophy; nor is it, for that matter, exclusively a mesodermal disorder; ectodermal structures are involved as well. The emphasis laid on the skeletal changes influenced early writers in such a way that they failed to be impressed by the other aspects of this disease, which take this syndrome out of the limited region of chondrodystrophies into the group of disturbances in growth and development of the fetal mesoderm and ectoderm.

1. *Skeletal Manifestations.*—In all the reported cases a derangement in bone growth was present. This is considered of prime importance and an essential feature of this syndrome. The patients are usually referred to as the short-limb dwarfs (micromelia), because one or more of the extremities is shorter than normal; usually the proximal segment is shortened compared with the distal segment. The ends of the long bones are enlarged, and the visible joints are markedly swollen owing to the enlargement of the ends of the bones entering into their formation. The shape of the head is not characteristically affected; all shapes and sizes have been reported.

X-rays demonstrate a disturbance at the epiphyses in areas of enchondral ossification; they are markedly enlarged and deformed, with mushroom appearance,[14] and contain multiple discrete densities of various sizes which prove to be calcium deposits, giving the stippled appearance associated with this syndrome. Some of those who were able to follow their patients for a while reported a tendency for these centers to coalesce and become more irregular[11]; others reported definite improvement culminating in complete disappearance.[4,13] The x-ray appearance is characteristic and enables the radiologist to make the diagnosis in the vast majority of cases. Foci of calcium deposition are not limited to the epiphyses of the long bones; they have been reported in every bone in the body that develops through enchondral ossification—bones of the hand, the wrist, the ankle, the foot, the pelvis, the vertebrae, the intervertebral discs, the patella and the connective tissue around it, the mandible, and the rib cartilages—giving a variety of signs and symptoms referrable to the structures involved: short deformed digits; talipes calcaneovalgus; dislocation of the hip, of the fibula, and of the radius; kyphosis, and scoliosis.[5,6,8,11] It is of interest that calcium deposits have been found in the thyroid cartilage and the tracheal rings, as well as in the skin and synovial membranes.[15]

A prominent feature among the skeletal manifestations is the immobility of the joints and flexion contractures, leading in turn to almost complete immobility of one or more of the extremities. The joints are fixed in flexion and cannot be passively extended. This immobility was assumed to be due to the deformity present in the epiphyses; however, Lund[7] demonstrated at an autopsy of an infant that the normal structure of the skeletal muscles was completely replaced by tough white fibrous tissue. This accounts for their inelasticity and the contracture. This finding, together with normally appearing articular surfaces of the long bones, seems to indicate that the skeletal muscles may be primarily affected in this condition, producing a contracture and immobility of the joints. The neck is frequently affected and appears fixed in extension, simulating an opisthotonic posture.

2. *Skin Manifestations.*—The skin was reported in 10 cases to be thick, dry, and scaly; the skin of the palm was reported to be markedly thickened, deeply furrowed, and adherent to the deep tissues. Cream-colored horny patches that could be detached with or without leaving a bleeding base were reported by Bloxsom.[4] These manifestations tend to improve with time, and the skin begins to assume normal appearance.[4,11]

3. *Ocular Manifestations.*—Bilateral congenital cataracts were noted in 14 of the cases reported. Only in three was there a mention that they were absent at the time of examination; the rest failed to mention whether cataracts were looked for at all. The cataracts may be present at birth or may develop during the first year of life [4]; they may assume the appearance of a dense nuclear cataract with peripheral radiating spokes or a complete opacification of the lens. Only one attempt at needling the cataracts was made,[4] which resulted in a dense membrane occupying the pupillary area. The presence of cataract is of great diagnostic and prognostic value; its presence rules out the milder congenital anomalies of bone growth that carry usually a good prognosis, such as fetal chondrodystrophy and dysplasia epiphysealis multiplex and stippled epiphyses of the acquired variety. In all cases, patients reported to have cataracts died before the age of 2 years.

4. *Cardiac Involvement.* — Congenital heart defects were reported in six cases; these included interventricular septal defects, valvular defects (see below), and patent ductus arteriosus.

5. *Manifestations Referable to the Gastrointestinal Tract.*—The majority of the cases were first brought to the attention of the physician for one of the following reasons: (*a*) lack of normal growth and gain in weight despite good intake; (*b*) inability to take the formula (some choked to death during feeding); (*c*) vomiting and diarrhea of no demonstrable etiology.

6. *Mental Deficiency.* — Those patients surviving the first year of life exhibited marked mental retardation.

7. *General Weakness and Poor Resistance.*—There is failure to thrive in these children; they have weak voices and show no sign of activity or movement. In addition, they are remarkably vulnerable to the usual childhood diseases; the majority died of upper respiratory infections; one died of miliary tuberculosis.[17]

Laboratory Studies

Studies of the blood calcium, phosphorus, alkaline phosphatase, cholesterol, and urea nitrogen failed to demonstrate any consistent significant deviation from normal among the cases reported. Urine was normal, and the Wassermann reaction was negative.

Onset and Clinical Course

It is established that this defect starts in utero and that the well-developed picture of this syndrome may be present at birth. Eighty per cent of the reported cases were brought to the attention of the physician before the age of 9 months; only three were seen after the age of 2 years, and only one at the age of 9 years. Lack of growth, physical deformity, and feeding difficulty were the things that caused the child to be brought to the physician. The disease usually follows a rapid course for the worse and ends fatally, in the vast majority of cases, before the age of 2 years. However, Raap [13] reported improvement in the bone changes during a four-year follow-up, with reduction of the stippling and progress of the epiphyses towards a normal x-ray appearance and normal growth. Bloxsom [4] reported a similar improvement in the x-ray appearance of the skeletal manifestations over one year of observation. It is conceivable that different grades of severity exist, but, judging by the course of the cases reported, the prognosis is very poor.

Pathology

1. *Bone.*—There is agreement on the description of these lesions at autopsy. Harris [16] reported absence of the usual pattern of orientation of the cartilage cells and of the process of calcification and ossification in the region of the epiphyses in areas of enchondral ossification; the cells were irregularly distributed. There were patchy areas of mucoid degeneration with cyst formation and deposition of calcium in and around these areas, which were or

were not invaded by granulation tissue. He insisted that these findings were identical with what he saw in the achondroplasias. However, Fairbank [20] and others felt that achondroplasia follows a pattern which is true to type and is identical in all the reported cases and which is entirely different from that encountered in this syndrome; also, the shafts of the long bones are involved in the achondroplasias. They felt that the two conditions, though giving a similar pathologic appearance, are best considered to be separate entities.[3]

Schönenberg [11] described pleomorphism of the cartilage cells with softening and hydration of the ground substance and formation of cystic spaces, around which was laid a mosaic of foci of calcification without any pattern; these areas were surrounded by vascularized granulation tissue, with giant cells and osteoclasts.

Tisdall [12] reported dead cartilage cells with shrunken nuclei, granular and vacuolated ground substance with fatty degeneration and calcium deposition, and a surrounding foreign body reaction.

All authors agree that the subperiosteal ossification in these cases is perfectly normal.

2. *Muscle.*—Lund [7] was the only one to mention the pathologic findings in the skeletal muscles; these have already been mentioned above and consist of complete replacement of the muscle fibers by tough white fibrous tissue.

3. *Connective Tissue.*—Areas of mucoid degeneration and hydration of the ground substance with formation of cystic spaces and deposition of calcium in the subcutaneous connective tissue have been described.[11,12]

4. *Mitral Valve.*—A similar pathologic change has been found in the connective tissue at the base of the mitral valve, with calcium deposition.[12]

5. *Skin.*—The skin lesions were biopsied in some cases, and the pathologic picture was that of dyskeratosis.[4,11]

6. *Gastrointestinal Tract.*—There is no mention of the findings in the gastrointestinal tract at autopsy.

Differential Diagnosis

It is extremely important to differentiate this condition from other congenital anomalies, because the prognosis for life and normal growth in this condition is poor, while it is good in the other anomalies.

The first to be differentiated is benign casual stippling or calcium deposits at the ends of long bones and some joints, encountered in the adult where the stippling is not associated with enlargement of the epiphysis or disturbance in bone growth and where everything else is perfectly normal.

The second condition is fetal chondrodysplasia, where the x-ray picture and the involvement of other mesenchymal structures might be confusing; yet the presence of normal muscle size and strength and normal or unusually free mobility of the joints, with normal skin and appendages and lack of involvement of any ectodermal structure, together with the absence of congenital cataract and mental retardation, make the diagnosis possible.

The third condition is dysplasia epiphysealis multiplex; in it the x-ray appearance may or may not be very different from that of chondrodystrophia congenita calcificans punctata; typically, however, there is mottling and irregularity of the epiphysis, in contrast to the very discrete, sharply outlined stippling and enlargement of the epiphysis. The absence of other mesodermal or ectodermal involvement and the absence of cataracts, together with normal mental development, make the differentiation possible.

Etiology

The etiology is not known.

Several hypotheses have been offered; Bloxsom [4] found a high blood calcium during the first three days of life and felt that fetal hypercalcemia, induced by a change

in the permeability of the placental barrier, would lead to deposition of calcium in the fetal tissues. However, hypercalcemia alone cannot explain the various manifestations of this syndrome, and a high blood calcium level was not encountered in any of the remaining cases. It is of interest that the placenta in this case was perfectly normal, grossly and histologically.

Wilkins[21] was impressed with the response of hypothyroid children to thyroid therapy. Normally, the epiphyses start to ossify and deposit calcium at a definite age, different for different bones. This process is markedly retarded in hypothyroidism. If thyroid extract is given, the epiphyses in which ossification was delayed develop multiple centers of calcium deposits, giving an x-ray picture similar to that seen in this syndrome. These multiple centers fuse with time, so that the epiphysis during thyroid therapy proceeds to normal appearance and growth. Ossification in the uninvolved epiphyses proceeds normally, without multiple foci of calcium deposition. Wilkins felt that hypothyroidism was at the basis of this disorder because of the similarity of the x-ray pictures. However, the course in chondrodystrophia calcificans congenita is entirely different; the calcium deposition is premature instead of being delayed, and the extraskeletal pathology cannot be explained by this hypothesis. Hypothyroidism was not demonstrated in any of the cases reported, and thyroid extract, when given to these patients, did not influence the course of the disease or the appearance of the epiphyses or their growth.

The etiology of this syndrome with its polymorphous manifestations rests obscure.

Treatment

Treatment has been palliative and symptomatic. Thyroid extract was tried without any effect; recently[9] corticotropin (ACTH) has been tried, without any noticeable influence on the course of the disease.

Report of Cases

CASE 1.—The patient was first seen in the pediatric service of the S. U. I. Hospitals in December, 1955, for poor weight gain, recurrent vomiting, and "stiffness" of the extremities since birth.

1. *History.* — Delivery was full-term spontaneous, and unaided; birth weight, 2800 gm. At that time the mother noticed "stiffness" of the boy's extremities and digits in a flexed position and a slight enlargement of the knee joint.

At the age of 6 days he was hospitalized for four days, for severe vomiting and dehydration, which were partially controlled by fluids intravenously and a change of the formula. Vomiting persisted in a mild form despite trying five different formulas, and weight-gain was very slow. The stools were of normal frequency and consistency.

When the patient was 3 months old, the pediatrician noticed marked enlargement of the knee joints and further limitation of passive movement of all joints.

At the age of 5 months bilateral cataracts were diagnosed.

Since birth the child assumed one position, which he hardly ever changed of his own accord, and he would cry if placed in any other; he preferred lying on the right side with the neck extended, the legs flexed and crossed, and the arms flexed, and the right thumb was occasionally made to reach the mouth. He did not seem to be in pain. He would remain in this position all the time, without exhibiting any form or degree of movement of the arms or legs; he neither kicked nor rolled over, and he had very poor head control when held erect. The mother was not certain as to whether he had any vision or not; at times he would follow light, and at others he would maintain a blank gaze. Vomiting and poor weight-gain continued till the present admission.

2. *Family History.*—Father and mother living and well; no intermarriage or history of maternal infection during pregnancy. The patient has two sisters, one 7 and the

other 4 years old, with perfectly normal health and growth.

3. *Physical Examination.*—A 10-month-old white boy, markedly small, lying quietly in a slightly opisthotonic position, exhibiting no movement of the extremities or digits other than the occasional sucking of the right thumb. Length, 70 cm.; weight, 5800 gm.; pulse rate, 120 per minute; respirations, 32 per minute.

(*a*) Integument: Maculopapular eczematous rash over left cheek.

(*b*) Lymphatic system: Palpable firm inguinal nodes.

Fig. 1.—Photograph of the first patient in recumbent position, with slight turning to the right side. Note extension of the neck, shortness of arms and thighs, and enlargement of the knee and the elbow joints, with flexion contractures and scissors legs.

(*c*) Skeletal System: (1) Head. Symmetrical; circumference 40 cm.

(2) Upper extremities. The arm was markedly shortened compared with the forearm, with slight enlargement and flexion contracture of the elbow joint which could not be passively extended beyond an angle of 150 degrees. The phalanges are long and slender, with moderate enlargement of the joints.

(3) Lower extremities. The proximal segment was shorter than the distal segment; there was resistance to passive abduction of the hip, which could be abducted only 45 degrees. The tibia was bowed, and the knee joint, markedly enlarged, with absence of ballotement or positive transillumination. It could be passively extended to a maximum of 100 degrees only. The ankles possessed normal mobility.

(4) Trunk. Slight kyphosis of the thoracic segment and definite resistance of the neck to mobilization from the extended position.

(*d*) Muscular System: Marked atrophy of the muscles of the legs, arms, and forearms.

(*e*) Eyes. Normal lids, conjunctiva, and cornea. The pupils were round and regular and reacted to light both directly and consensually; they dilated readily and widely with phenylephrine (Neo-Synephrine) hydrochloride 10% drops. The lens was completely opaque, including the most peripheral and superficial layers of the cortex. The fundi could not be seen.

(1) Vision. The child seemed to follow light more often than not. There was no spontaneous nystagmus; the relative position of the eyes was normal.

(2) Tension. Normal by digital palpation.

(*f*) Nose and Ears: Normal.

(*g*) Mouth: Normal dentition for the age. A questionable submucous cleft palate.

(*h*) Chest: Symmetrical. Circumference 40 cm.; superficial veins were dilated and seemed to fill from below. Lungs were

resonant and clear. Heart sounds, boundary, and rhythm were normal.

(*i*) Abdomen: There was a small umbillical hernia; otherwise, no palpable masses or tenderness.

(*j*) External Genitalia: Normal male.

(*k*) Nervous System: Neurological examination revealed no abnormal findings.

(*l*) Laboratory Studies: (1) Blood. Repeated determinations (at least three times) gave normal values for the following: complete blood cell count and differential count, proteins, albumen-globulin ratio, calcium, phosphorus, alkaline phosphatase, protein-bound iodine, blood urea nitrogen, creatinine, uric acid, fasting blood sugar, sodium, potassium, chlorides, CO_2-combining power, and thymol and zinc turbidity tests. The only abnormal finding, which was present on six determinations, was the serum cholesterol, where there were values as low as 62 mg/100 cc. for total cholesterol and 31 mg/100 cc. for cholesterol esters.

(2) Urine. Results of routine examination and microscopic study were normal. Electrophoretic studies for urine amino acids revealed normal constituents.

(3) Stools. Normal microscopic findings. A metabolic study over a three-day period for calcium uptake and excretion revealed no significant deviation from normal.

(4) EKG. Normal.

(*m*) X-ray Studies: (1) Skull. Normal.

(2) Chest. The heart, great vessels, and lungs were normal.

(3) Vertebral column. Calcifications in the vertebral bodies.

(4) Ribs. The vertebral ends were flared and showed dystrophic changes.

(5) Upper extremities. There was stippling of all the epiphyses, with flaring of the epiphyseal portion of the shafts of the long bones, particularly of the humeri, with shortening of the diaphyses; there was calcium deposition around the shoulder joint.

(6) Lower extremities. Similar changes at the epiphyses of the long bones, with flaring and stippling, especially of the femora, which were shortened. The ankles and metatarsals were normal.

4. *Diagnosis.* — (1) Chondrodystrophia congenita calcificans punctata, with bilateral cataracts, and (2) infantile eczema.

Fig. 2.—X-ray picture of the upper extremities and trunk of the first patient. Note shortness of both humeri, marked mushrooming of both epiphyseal ends, and fine "stippling" due to calcium deposition in the epiphyseal region. Also note the flaring of the vertebral heads of the ribs.

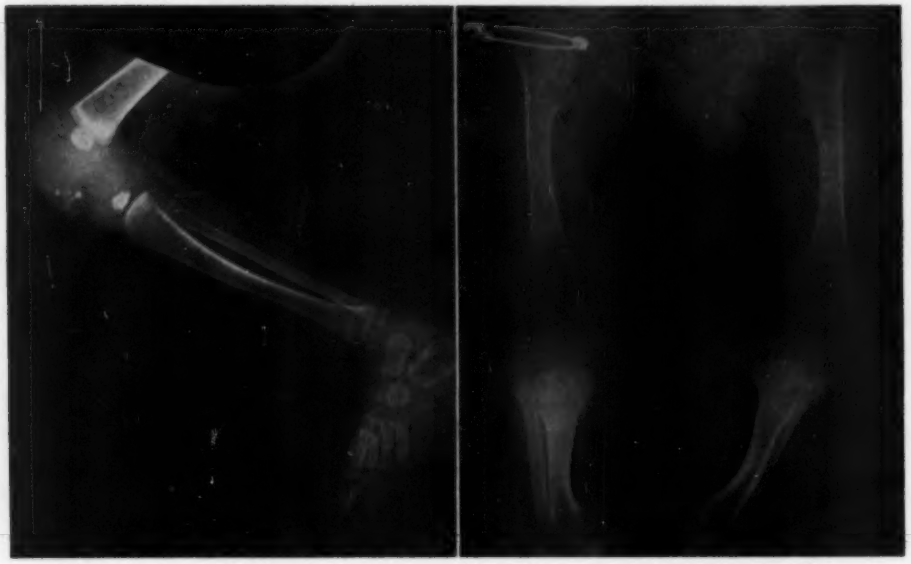
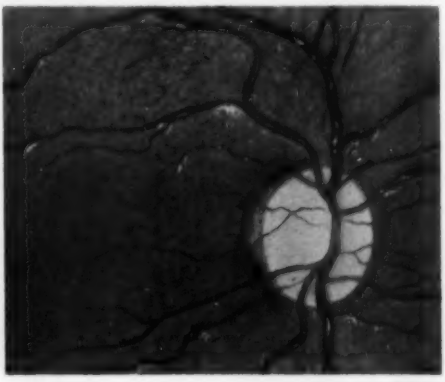


Fig. 3.—X-ray picture of the lower extremities of the first patient (posteroanterior and lateral views). Note the marked mushrooming of both ends of the femora and those of the tibias, with fine discrete "stippling" in the epiphyseal regions. In the lateral view, notice, in addition, the abundant fine stippling around the patella and in the synovial membrane.

5. *Treatment and Course.*—The child was transferred to the eye service, where bilateral needling was performed under general anesthesia in January, and he was discharged after five days, to be given further treatment with atropine 1% drops. He was seen in February with bilateral purulent otitis media which required myringotomy for its control; at this time the eyes were quiet, but the cataracts showed no sign of progress or resorption, and on Feb. 25 another bilateral needling was performed under general anesthesia. In March he was seen with quiet eyes, with a few cortical remnants occupying part of the pupillary opening, through which the fundi could be seen. The optic nerves were pale white, with sharp borders, and the retinas had a granular appearance. X-rays of the skull at this time revealed no abnormal findings. The patient was seen two months later with two wide pupillary openings through which the previous findings in the retinas and optic nerves were confirmed; the mother reported no special change in vision, and we failed to demonstrate satisfactorily any consistent following of light. He had normal pupillary response to light. At this time the x-rays were repeated, and no appreciable change in the bony findings were detected as compared with films taken six months previously. The optic foramina

Fig. 4.—Drawing of the right fundus of the first patient. Note the marked optic atrophy of the primary type and the granular appearance of the retina.



were of normal caliber and patent, and so were the orbits. There was a definite closure of the posterior saggital sutures by x-ray, and the vertebral bodies were biconcave.

At this time the pediatric evaluation indicated definite mental retardation, subnormal height and weight, premature closure of the posterior saggital suture, and normal dentition.

Complete x-ray studies of the parents and the two sisters revealed normal skeletal framework.

CASE 2.—The following case is reported despite the short period of observation because of some interesting clinical and biochemical findings.

The child was brought at the age of 2 months to the orthopedic service because of shortening and deformity of the right lower extremity since birth. Other salient points in the history were the following: 1. Areas of redness, thickening, and roughness of the skin over the right thigh and abdomen which were noticed at birth and had improved since to simulate normal skin. 2. Feeding problem since birth; projectile vomiting followed every meal. Breast feeding was replaced by a variety of formulas, until "Similac" seemed partially to control the condition. Had normal weight gain. 3. Epiphora in the left eye since birth; during the last three weeks the eye became red, with purulent discharge.

The physical examination revealed the following positive findings in this 2-month-old girl.

Integument. The skin over the right thigh and buttock was rough, scaly, and thickened; there was no discoloration.

Skeletal system. The arms were shorter than the forearms. The right leg was 2 in. shorter than the left and was held at the hip in 30 degrees of flexion and 30 degrees of abduction with external rotation. There was flexion contracture of the right knee.

Eyes. There was purulent dacryocystitis, left; there were no cataracts. Normal fundi O. U.

X-ray findings were multiple punctate centers of ossification in all epiphyseal locations throughout the entire body. The right hip was subluxated.

Blood, urine, and stool studies. Determinations similar to those performed on the first case were done and revealed no abnormal finding other than the cholesterol level, which was consistently low; an average value of the total cholesterol was 117 mg/100 cc.

The dacryocystitis was treated by irrigation with penicillin solution, 10,000 units/cc., and one probing of the lacrimal passages, which overcame an obstruction in the nasolacrimal duct, and the condition was brought under control. The hip was treated conservatively. When the patient was seen two months later, the epiphora had disappeared.

Comment

A review of the world literature revealed that the two cases reported in this paper present some unique findings that have not been described as associated with this syndrome in any of the cases reported to date; a discussion of these findings and their possible significance is warranted.

1. *Primary Optic Atrophy.*—Soon after the second needling of the cataracts in the first patient examination of the fundus became possible and revealed marked bilateral optic atrophy of the primary type and granular appearance of the retina. At that time x-ray studies of the orbits and skull showed the orbits and optic foramina to be of normal size and shape, and the posterior sagittal suture was patent, ruling out the possibility that the optic atrophy might have been due to pressure from the neighboring bony structures because of a faulty development.

This finding of bilateral optic atrophy poses two questions of great interest. (*a*) Is the optic atrophy noted in this case a part of the syndrome, or is it an independent and coincidental congenital defect? (*b*) If it is a part of the syndrome, then is it

only an isolated involvement of the optic nerve or merely a part of a more generalized involvement of the central nervous system, such as lack of development of the cerebral cortex?

Unfortunately the answers to these questions cannot be arrived at with the desired degree of certainty because of the lack of information in the literature regarding the status of the retina, the optic nerve, and the central nervous system. However, an analysis of the available information proves helpful.

The findings of the ocular examination were mentioned only in 17 of the 31 cases reported; of these, 14 had cataracts and visualization of the fundus was not possible and only in 1 of the remaining 3 was the fundus examined and reported to be normal. There has been only one attempt at needling these cataracts,[4] and it resulted in a dense pupillary membrane which made fundus examination impossible. We can summarize by saying that we have no information about the fundi in 30 of the 31 reported cases.

The incidence of idiopathic congenital bilateral optic atrophy in the general population is extremely low, and so is the incidence of chondrodystrophia calcificans congenita punctata. Although, theoretically speaking, it is conceivable to have these two rare conditions exist independently of each other in one patient; yet from a statistical point of view this possibility is very remote, and one is more justified in considering this finding as a part of the syndrome rather than as an independent coincidental congenital defect until a more thorough examination of patients with this syndrome in the future proves the contrary.

The second question cannot be answered with the same degree of assurance as the first; however, a study of the information available makes one lean toward accepting the second clause of this question. Marked mental detardation was present in the vast majority of the reported cases in which the patients survived the first year of life. No information about the fundi of these cases is available, nor is there any mention in the reported autopsies of the status of the central nervous system. Unfortunately, the attempt at gaining some information about the cerebral cortex in the first patient was thwarted by the parents' refusal to grant permission for pneumoencephalography and ventriculography, but the clinical evidence, i. e., the marked mental retardation associated with this syndrome, offers some grounds for such a speculation, which is worth keeping in mind to verify whenever a more direct means of study of the central nervous system becomes feasible in the future cases.

2. *Involvement of the Membranous Bones.*—It is emphasized by all authors that the pathologic process in the skeletal framework is manifested only in the regions where bone development follows the path of enchondral ossification. The first patient developed premature closure of the posterior sagittal suture, diagnosed by the x-ray appearance of this area, which became progressively more impressive on two follow-up checks at three-month intervals. Again one is faced with the first question I discussed when I considered the optic atrophy; here, however, more support is given by knowledge of the generalized nonspecific effects of this disease process, which are by no means exclusive or specific to the epiphyses but include cartilage, ground substance, connective tissue, muscle, and such unrelated ectodermal structures as the skin, the lens, and the optic nerve. In the light of the available information it is not surprising that this disease should involve the membranous bones; rather more surprising would be the emphasis that it always spares them.

3. *Low Cholesterol Level.*—In the two cases reported in this paper the level of the total cholesterol as well as of its free esters was consistently and significantly low as compared with the average normal for this age group. The significance of this finding is not clear; whether it is a primary

factor or a secondary manifestation is difficult to tell from the present understanding of the metabolism and function of cholesterol. The liver-function tests gave normal results. The low cholesterolemia speaks against Wilkins' hypothesis that a hypothyroid state is the etiologic basis for this syndrome.

Summary

Two cases of chondrodystrophia calcificans congenita punctata are reported.

A review of the world literature revealed that 31 cases belonging to this syndrome have been reported to date under a variety of names that emphasize the x-ray appearance of the involved bones. I cannot escape the feeling that this emphasis in the nomenclature unfortunately prejudiced the early reporters in such a way that information regarding the extraskeletal manifestations of this syndrome was either lacking or inadequately investigated and reported. A study of the assembled manifestations which were reported as associated with this syndrome reveals that this syndrome involves the cartilage, the subcutaneous connective tissue, the heart, the gastrointestinal tract, the central nervous system, the skin, and the eyes. Such findings take this syndrome out of the limited category of chondrodystrophies into that of a more generalized disturbance, which can interfere with the normal growth and development of mesodermal as well as ectodermal structures.

The syndrome starts in utero, and the well-developed picture may be present at birth. No definite statement can be made regarding the sex incidence or the familial incidence of this disease.

The clinical picture is characterized by skeletal deformities, lack of normal growth of the skeletal framework, nutritional problems such as inability to gain weight despite adequate intake, persistent projectile vomiting and diarrhea of unknown etiology, marked mental retardation, marked reduction in resistance to the usual childhood infections, dyskeratosis of the skin, congenital heart defects, and bilateral congenital or developmental cataracts.

The x-ray picture of the epiphyses is characteristic. There is marked enlargement and mushrooming of the epiphyses with multiple discrete punctate densities due to calcium deposition in these areas, giving them a "stippled" appearance.

The disease progresses to the worse. Few authors have reported improvement in the bone and skin changes over a period of observation.

In contrast to other chondrodystrophies, this syndrome has a poor prognosis for life and for normal skeletal growth. The vast majority of the reported patients died before the age of 3 years. The severity and extent of involvement may vary in this syndrome without influencing the over-all prognosis, once the diagnosis is established.

Clinical and laboratory studies have not revealed any significant deviation from normal in any of the tests performed.

The etiology is not known, and the pathogenesis of this syndrome is not understood. Treatment has been palliative and of no effect on the progressive course of the disease or its manifestations.

The ocular manifestations are of prime importance in the differential diagnosis and prognosis of this disease. Bilateral cataracts may be present at the time of birth or may develop during the first year of life. Their presence completely rules out the other chondrodystrophies that might present a similar x-ray picture and that have a good prognosis for life and bone growth, such as fetal chondrodysplasia, dysplasia epiphysialis multiplex, and the benign casual "stippling" occasionally reported by the radiologist in an otherwise normal person. The presence of cataracts carries a poor prognosis; all patients with cataracts died before the age of 2 years and exhibited a very severe form of the disease.

The two cases reported in this paper presented some unique manifestations not reported before as associated with this syndrome; these were bilateral primary optic

atrophy, involvement of the membranous bones, and a persistent significant lowering of the blood level of both the total cholesterol and the cholesterol esters. The significance of these findings is discussed.

In conclusion, it is the main purpose of this report to show that this syndrome, despite the names attached to it, is one that has polymorphous manifestations, the limits and extent of which have not been adequately investigated. In the light of the information collected from the literature it seems appropriate and justifiable to think of the pathologic process in this disease as one which can interfere with the normal growth and development of the fetal mesoderm and ectoderm, rather than as one which specifically affects the epiphyses in the bones that develop through enchondral ossification. This broad orientation is more apt to lead us to the right approach towards the understanding of this syndrome and its relation to other congenital diseases.

The ocular manifestations are not only of academic interest but are also of great importance in making a differential diagnosis and prognosis in this disease.

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Vogt-Koyanagi-Harada Disease

Treatment with Prednisone

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A prodromal meningismal episode, followed by nontraumatic bilateral uveitis, followed later by vitiligo, alopecia, dysacousia, and poliosis are the essential features of the Vogt-Koyanagi syndrome.[1] If retinal detachment is detected in the course of the illness, the diagnosis has been made of Harada's disease.[2,3] Recent authors, however, describe these syndromes as variations in severity of a single disease.[4,5] This report presents a case of severe headache, nausea and vomiting, and bilateral nontraumatic uveitis followed in several months by the appearance of poliosis and alopecia. This case is noteworthy for its features of both the Vogt-Koyanagi syndrome and Harada's disease, for its successful outcome under therapy, and for an unusual problem of differential diagnosis.

Report of a Case

A 36-year-old white woman was admitted to the neurological service complaining of headaches and nausea and vomiting of two weeks' duration. There was bilateral edema of the optic nerve heads. In an observation period of two weeks upon the neurological service, visual fields showed increasing enlargement of the blind spots and gradual constriction of the central fields. The peripheral fields remained full and complete (Fig. 1).

Examination of the fundus revealed increasing edema about the optic nerve head, with retinal edema gradually impinging upon the maculae. Pulsations of the veins were absent. Veins were distended. Neither hemorrhages nor exudates were found about the disc or in the periphery. Vision was reduced from 20/30 upon admission to 20/70. Focal neurological signs could not be elicited. Study of the spinal fluid in this period revealed normal pressure, six white blood cells on two different occasions, and normal values for chemical components.

Results of the remainder of the physical examination and laboratory studies were normal, except for what appeared to be old healed lung disease.

In view of decreasing vision, increasing size of the blind spots, increasing edema of the optic nerve heads, progression of retinal edema, and continued headache and vomiting, a ventriculogram was performed. A posterior fossa tumor was suspected. At operation the brain was noted to be under normal tension and pulsating well. The cerebrospinal fluid was clear and colorless. No obvious abnormality was noted in the visible cerebral cortex. No significant abnormalities of the ventricular system were noted.

On the second postoperative day cloudy spinal fluid was obtained. For the next 12 postoperative days, 100 to 500 white blood cells were found in the spinal fluid, with decreased sugar. Alpha-Streptococcus was cultured. This is not a usual skin or laboratory contaminant. In view of the decreased sugar and large number of cells, it was felt that this bacterial meningitis was not related to the basic problem but was secondary to the operative procedure. The patient was maintained on antibiotics for 20 days after the operation.

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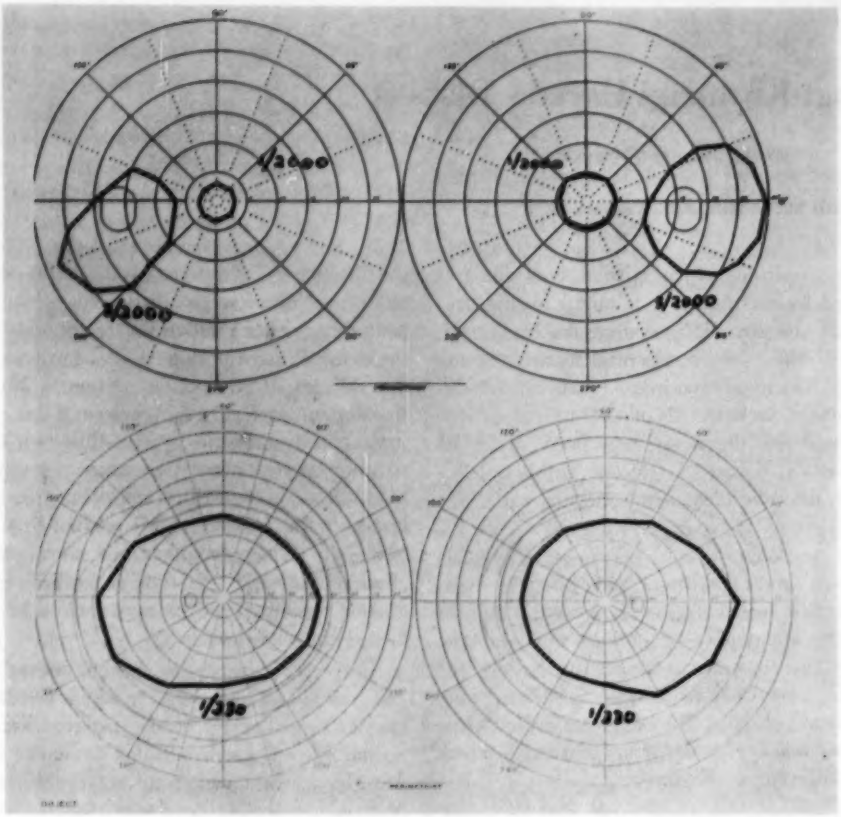

Fig. 1.—Visual field examination, in the second week of the disease, revealed enlargement of the blind spots and constriction on the central fields. The peripheral field remained full and complete.

Five days after the ventriculogram, and six weeks from the onset of symptoms, an intense flare was seen in the anterior chamber of both eyes, with many large keratitic precipitates. Synechia had already begun to form. The media were cloudy, and the retina could not be seen distinctly. Vision was reduced to 20/100 in both eyes. Atropine and topical cortisone were instituted. Three days after the onset of the anterior uveitis, which was the eighth postoperative day, the patient was given oral prednisone (Meticorten), 20 mg. a day in divided doses. On the 12th day of steroid therapy vision had improved to 20/50. The fundus could be visualized, with much retinal edema, and blurring of both disc margins. The patient was discharged one month after the onset of the uveitis, with 20/30 vision. There were only occasional cells in the anterior chamber. Disc margins were well defined, and retinal edema had subsided.

One month after discharge the patient complained of puffiness of her face. The prednisone was reduced, gradually, to 10 mg. daily. In three weeks the patient presented herself at the clinic with vision of finger counting in both eyes at 2 ft. (60 cm.) and severe flare through which the retina could not be visualized. The patient was readmitted to the eye service. The dosage of prednisone was then raised to 30 mg. a day. Response was rapid. Only occasional

Fig. 2.—Whitening of lashes was seen in the fifth month of the disease.

Fig. 3.—Examination of patient's scalp showed marked thinning of hair.

cells were noted in six days, with vision improved to 20/40. The patient was discharged in two weeks. Within one month of the second attack, vision had returned to 20/30.

The patient was maintained on prednisone for the next 11 months, 30 mg. daily for 4 months and then 20 mg. daily for the remaining 7 months, after which the drug was gradually withdrawn.

Vision remained at 20/30. Fundus examination revealed a sharp disc. At the macula there was a mottled area in both eyes, with scattered pigmentary changes. Blind spots showed only slight residual enlargement, with a normal peripheral field.

About the fifth month of the disease, whitening of the lashes was seen (Fig. 2). Examination of the patient's scalp showed incomplete regrowth of hair since the craniotomy and considerable thinning (Fig. 3). Eyebrows were particularly thin (Fig. 4). The patient had no hearing complaints. However, audiometric examination revealed a 30 db. hearing loss in both ears, but this was not consistent with nerve loss.

Fig. 4.—In addition to thinning of hair, eyebrows were particularly sparse.

Comment

When one is confronted with a case of nontraumatic bilateral uveitis, followed by the later appearance of poliosis and alopecia, two diagnostic possibilities may be entertained: that is, Harada's disease or the Vogt-Koyanagi syndrome. The diagnosis of either disorder seems to depend upon the occurrence of retinal detachment, anterior or posterior uveitis, and the occurrence of alopecia or poliosis.[5]

Retinal detachment is regarded as diagnostic of Harada's disease.[6] This feature is far from clear. Detachment was not reported in 4 of Harada's original 12 cases.[2] In contradistinction, there are several reviews in which detachment is reported in cases called the Vogt-Koyanagi syndrome, including a case of Koyanagi's.[4,7]

Severe anterior uveal involvement is regarded as characteristic of the Vogt-Koyanagi syndrome, in contrast to posterior uveal disease in Harada's disease.[1,3] Yet anterior segment disease has been encountered in half the cases of Harada's disease reported in English.[5] Whether posterior disease in the Vogt-Koyanagi syndrome is obscured by anterior uveal involvement is only conjectural. In fact, it is suggested that retinal detachment in Vogt-Koyanagi disease is not detected, since it may not be visible through media which block a view of

the fundus.[5] Prognosis of both diseases seems to hinge upon anatomical localization. Anterior disease with secondary glaucoma, cataracts, and membranes in the Vogt-Koyanagi syndrome offers far less chance for recovery of satisfactory vision than Harada's disease in which the retina may reattach spontaneously.[5]

Alopecia and poliosis is noted as an invariable feature of the Vogt-Koyanagi syndrome.[6] Still, in a large percentage of reported cases these signs were not present.[1,4] On the other hand, poliosis was noted in Harada's original series.[2]

The two diseases run parallel courses.[5] Maintaining that these are separate disease entities becomes very questionable. There is a meningeal period of about two weeks to a month, an ophthalmic period of three to five months, and a convalescent period of one-half to one year.[5] In the prodromal meningeal period there are complaints of vertigo, nausea, drowsiness, fever, orbital pain, and vomiting.[2,4] This is followed by the appearence of eye disease. The onset may be gradual, with cells in the anterior chamber, or fulminating, with bulbar injection, turbidity of the media, keratic precipitates, choroiditis, optic neuritis, and retinal edema.[6]

In both diseases, shortly after the appearance of the uveitis, dysacousia and retinal detachment may occur.[5] Retinal detachments occur in the first few weeks, having been reported in both diseases.[4] Several weeks to months following the appearance of the uveitis, poliosis, vitiligo, and alopecia may be noticed. The disease may run a course of a year or longer. Complications of the Vogt-Koyanagi syndrome and Harada's disease are complete detachment, secondary glaucoma, cataract, phthisis bulbi, and atrophy of the globe.[1]

When the essential features of the course of this case are reviewed, it is noted that both an anterior and a posterior bilateral uveitis were diagnosed. Posterior involvement was noted much earlier. The posterior fundus was soon lost to view. The appearance of poliosis and alopecia later in the disease suggested the diagnoses. When it is noted that retinal detachment could have been present, that there was both an anterior and a posterior involvement, and that alopecia and poliosis are not determining factors, it is questionable whether to report the case as Vogt-Koyanagi syndrome or Harada's disease. Rather, evidence is presented of the similarity of features which may exist in the same disease.

The unusual onset of this disease caused much concern. The patient presented the signs and symptoms of an expanding intracranial lesion. Headache, nausea, vomiting, bilateral edema of the optic nerve heads, increasing enlargement of the blind spots, and decreasing vision indicated exploration, in order. The onset of Vogt-Koyanagi-Harada's disease, with papillitis, may resemble the papilledema of increased intracranial pressure.

Crawford,[8] in 1953; Stadnik and McFadden,[9] in 1954, and Cordes,[10] in 1955, have all reported the use of cortisone in cases of Harada's disease. Crawford [8] reported beneficial effects in a single case, but he lost careful management of the patient and was unable to bring the disease under control when steroid therapy was resumed. He suggested that steroids be used for a prolonged period. Stadnik and McFadden [9] continued steroid therapy for 10 days, thought there was aggravation of the disease, and discontinued its use. Cordes [10] reported no effect at all. In this case there was prompt suppression of the uveitis when prednisone was given. However, when the amount of prednisone was reduced, because of noticeable side-effects, there was reactivation of the disease process. Control of the uveitis was achieved again only when the amount of prednisone was increased to a therapeutic level. In the light of our experience in this case, it is suggested that steroids be maintained at maximum therapeutic dosage for a prolonged period.

Summary

A patient with bilateral edema of the optic nerve heads and striking symptoms of meningismus developed bilateral uveitis, followed by the appearance of poliosis and alopecia. The disease exhibited signs and symptoms of both the Vogt-Koyanagi syndrome and Harada's disease. There is considerable evidence that these are the same disease.

An early diagnosis of papilledema due to increased intracranial pressure was erroneously entertained in the presence of bilateral swelling of the discs, with severe headache.

The severe uveitis was favorably affected by the prolonged use of prednisone by mouth.

Dr. Samuel Gartner, Director of the Department of Ophthalmology, Montefiore Hospital, gave advice.

27 Ludlow St.

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Ocular Lesions Produced by Iodoacetate

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Introduction

Iodoacetic acid (IAA) in vapor form acts as a lacrimator (Mackworth [1]). When applied topically or injected into the corneal stroma, severe corneal lesions and opacifications may develop (Harley [2]).

In a series of papers, Noell [3,4] presented experimental evidence that intravenous IAA exerts a selective effect on structure and function of the retina. It impairs the electroretinogram (ERG) within a few seconds following its injection and produces death of the rod cells. This effect on the receptors of scotopic vision manifests itself microscopically as pyknosis of the rod nuclei and is followed by degeneration and atrophy of the outer retinal layers.

Similar to this effect of IAA on the retina are changes produced by high-intensity ionizing radiation in guinea pigs, rabbits, dogs, and monkeys.[5-8] From the similarity of the retinal changes produced by IAA and ionizing radiation, the question arose whether IAA also possessed the ability to induce lenticular changes resembling those observed following ionizing radiation. This might provide an important clue as to a possible common mechanism effective in both modalities of tissue trauma.

Nordmann and his associates [9] maintained calf lenses in a perfusion medium consisting of Tyrode glucose solution (1:1000) to which 4 gm. of monoiodoacetic acid was added. Clouding of the lens and subcapsular opacities were observed in vitro with the slit-lamp after two hours. The lactic acid content, the concentration of adenosinetriphosphate, and the amount of phosphocreatine were found diminished in the cataractous lenses as compared with control lenses perfused with Tyrode glucose medium alone.

In a preliminary report, Cibis and Noell [10] described the clinical and histological features of lenticular changes induced by intravenous injection of sodium iodoacetate in rabbits.

The present study was undertaken in an effort to confirm and amplify the preliminary data and compare the ocular lesions produced by iodoacetate with those described following radiation.[20] Therefore, particular attention was directed toward (*a*) the inflammatory response occurring in rabbit eye following intravenous injection of IAA, (*b*) the effect of IAA injection upon the mitosis of lens epithelium, (*c*) the effect of IAA upon the rate of secretion of aqueous humor, and (*d*) the pathogenesis and morphology of IAA-induced cataractous changes.

Methods

The sodium salt of iodoacetic acid (IAA) neutralized to pH 7.4 with dilute NaOH was injected in doses of 20 mg/kg. body weight into the ear veins of 2-3 kg. male albino rabbits.

The total doses administered varied from 20 to 60 mg/kg. A second injection was given after 6 hours and a third after 24 hours in those animals receiving higher

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doses. Control animals of the same source, size, and sex were kept under similar environmental and nutritional conditions. They were killed at the same time as the experimental animals to secure comparable data for the evaluation of the effects under study.

In the first series of experiments concerning the acute effects of IAA upon the blood-aqueous barrier, a total of 16 rabbits was employed. Six animals received 20 mg. IAA; 10 animals, 40 mg/kg.

The animals were examined with the slit-lamp (Zeiss-Opton) every day over a period of 13 days. On the first day, the examinations were repeated hourly over a period of 6 hours and after 8 and 24 hours following the first injection. The technique of red reflex examination by transpupillary retroillumination with paraxial light beam of full strength and wide slit opening facilitated the recognition and estimation of cells which were found either floating or suspended in the anterior chamber fluid, adherent to the anterior lens surface, or suspended in the vitreous body.

In the second series of experiments, 10 animals were subjected to injections of 40 mg. IAA per kilogram. Three experimental animals were killed after 24 hours, two after 4 days, two after 8 days, and three after 12 days. Equivalent numbers of controls were employed. The anterior chambers were tapped with a Kinsey pipette immediately after death. An aqueous humor sample (0.030 cc.) was smeared on a glass slide and stained with Wright's stain for the purpose of cell counts.

The third series of experiments dealt with the effect of IAA upon the mitotic activity of the lens epithelium. For this purpose, a total of 41 experimental and 38 control eyes were used. The experimental animals were killed by air injection into the heart. Three animals were killed four to five hours and three, six to eight hours, after injection of a single dose of 20 gm. per kilogram. All the other experimental animals received two injections of 20 mg/kg., six hours apart. They were killed as follows: three animals after 24 hours, and five after 2 days, five after 16 days, five after 32 days, and five after 60 to 120 days. Mitotic activity was estimated by the total count of mitotic cells per flat preparation of the entire lens epithelium. Cells in anaphase and early and late telophase were counted separately. Cells in the late telophase (separated cells not included) constituted approximately 90% of these cells. The flat preparations of the lens epithelium were made according to the method of Howard as modified by von Sallmann.[16]

The effects of iodoacetate upon the rate of secretion of aqueous were studied by means of repeated tonographic tracings. An electronic tonometer with Leeds and Northrup recorder was used as previously described.[21] Tonograms were carried out before injection of 40 mg. IAA per kilogram and repeated at 48, 72, 120, and 168 hours after the injection. The rate of aqueous secretion was calculated from the intraocular pressure (P_o) and facility of outflow (C) values, assuming constant episcleral venous pressure of 9 mm. Hg.

The chronic effects of IAA on the rabbit lens were studied biomicroscopically in a group of animals comprising 32 experimental animals and an appropriate number of controls. Pertinent information concerning the doses of IAA administered, the total time of observation, and the incidence of IAA-induced lens changes can be obtained from Table 3.

The histological changes induced by IAA in rabbit lenses were studied in 36 eyes obtained from 18 animals. The freshly removed eyes were placed into Zenker's solution or in a 10% formalin solution for 48 hours or longer. They were embedded in either paraffin or celloidin, were cut in sections of about 15μ thickness, and were stained with hematoxylin and eosin.

Results

A. Inflammatory Reactions Following the Intravenous Administration of IAA.—

TABLE 1.—*Slit-Lamp Observation of Inflammatory Reactions Following Intravenous Administration of Sodium Iodoacetate in Rabbits*

Animals, No.	Dose of IAA, Mg./Kg.		Day After Injection											
			1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th
5*	0	A†	0/5	0/5											
10*	0	A	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
6	20	A	0/6	5/6											
		B	0	10^1											
		C	0	0											
10	40	A	0/10	5/10	6/7	7/7	7/7	5/5	5/5	5/5	5/5	3/3	3/3	3/3	3/3
		B	0	10^1	10^1	10^1	10^1–10^2	10^1–10^2	10^1–10^2	10^1	10^1	10^1	10^1–10^2	10^1	10^1
		C	0	0	0	0	10^1–10^2	10^1–10^2	10^1–10^2	10^1–10^2	10^1–10^2	10^1–10^2	10^1–10^2	10^1–10^2	10^1–10^2

* Controls.

† A, number of animals showing exudation (numerator) compared with number of animals alive (denominator); B, estimated number of cells in anterior chamber; C, estimated number of cells in vitreous.

The intravenous injection of IAA in form of its sodium salt affected the blood-aqueous barrier in rabbits in a fairly consistent and reproducible manner. Slit-lamp observations revealed the appearance of cells in the anterior chamber the second or third day following the first injection of IAA (Table 1). The number of cells increased subsequently, reaching a maximum at the fifth day. A plateau was maintained for about three days, i. e., until the eighth day. Thereafter, the number of cells seemed to decline gradually to less than 100. However, there were still many cells present in the anterior chamber of the animals which were alive at the 12th day following the first injection.

The cells appeared in groups pouring down from behind the pupil in the upper half of the anterior chamber. They were obviously entrapped in plasmoid or fibrinous fluid, as indicated by the drop-like arrangement and the slow speed with which they gravitated downward. They maintained a tendency to stick to the anterior lens surface after the downward movement became noticeably slow or ceased. This was usually the case when the pupillary center had been reached or surpassed. The pattern of lens-adherent exudates formed this way exhibited a characteristic uniformity similar to the pattern observed in experiments concerning the effect of low or medium doses of ionizing radiation upon the blood-aqueous barrier.

In the vitreous body, increased numbers of cells were observed with the slit-lamp from the fifth day on. A plateau of hundreds of cells was maintained beyond the 13th day of observation.

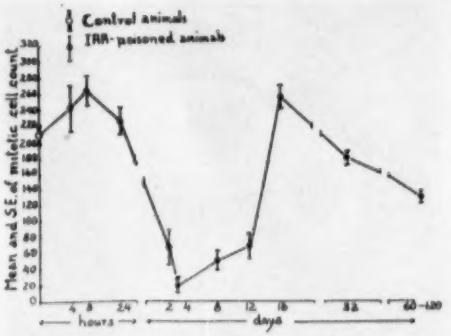


Fig. 1.—Effects of intravenous injection of 40 mg. sodium iodoacetate per kilogram of body weight on the mitotic activity of the lens epithelium in albinotic rabbits; 41 experimental animals and 38 controls were used. Vertical brackets indicate standard errors of standard deviations.

The histological examination of the aqueous smears stained with Wright's stain revealed that the majority of the cells in the anterior chamber consisted of erythrocytes mixed with a few lymphocytes and polymorphonuclear leukocytes. This is in contradistinction to the exudate produced by ionizing radiation, where the majority of cells consisted of polymorphonuclear and mononuclear cells.[20] The numbers of cells in the withdrawn fluid exceeded slit-lamp estimations. Anterior chamber fluid of control animals tapped in vivo was found to be essentially cell-free.

B. Effects of IAA on the Mitotic Activity of Lens Epithelium.—Data concerning the effect of IAA upon the mitotic activity of the lens epithelium are exhibited in Figure 1. They illustrate that during the first 24 hours, and under the conditions of our experiments, the mitotic activity was not impaired. Mitot-

TABLE 2.—*Iodoacetate Administration* and Aqueous Flow*

Time, Hr	Eyes, No.	P_o†	C	F	ΔF,%
0	37	19	0.33	3.3	..
48	34	17	0.30	2.4	−27
72	28	14	0.28	1.4	−58
120	17	17	0.38	3.0	− 9
168	16	19	0.36	3.6	+ 9

* 40 mg/kg. intravenously.
† P_o, mean value for intraocular pressure (mm. Hg); C, mean value for facility of outflow; F, mean value for rate of aqueous secretion (cu. mm/min.); ΔF,%, per cent change in rate of aqueous flow.

TABLE 3.—*Incidence of IAA-Induced Lens Changes (Vacuoles and Opacities) in Rabbits Observed with the Slit-Lamp*

Animals, No.	Na IAA, Mg./Kg.	Total Time Under Observation, Mo.	Incidence of Lens Changes	Intensity of Lens Changes*	Latent Period, Mo.
5	20	1-3	1	+	1.5
5	30	3	5	+-++	1.5
4	30	¾	2	+-++	3
6	40	1.5-2.5	5	(+)-+	1-1.5
4	40	7	4	+-+++	3
2	50	2	1	(+)	2
5	60	1.5-2.5	2	(+)	1.5-2
1	60	4	1	++	3
32	20-60	7	21 (65%)	(+)-+++	1-3

* (+), sutural opacities exaggerated; +, vacuoles and opacities in small numbers; ++, vacuoles and opacities in medium number; +++, vacuoles and opacities in larger number.

ic activity, however, was found inhibited in approximately 60% of the cases between the 2d and 12th days. This inhibition appeared to be a general effect, since the percentages of cells representing the various phases of mitosis maintained approximately the same ratio as those referring to the controls. Normal values were found after 16 days and later.

C. Aqueous Flow Following IAA.—Iodoacetate administration resulted in a partial suppression of the production of aqueous humor and a fall in intraocular pressure (Table 2). The rate of aqueous flow decreased appreciably by 48 hours and reached a minimum at 72 hours. Recovery was essentially complete at five and seven days, but there was considerable scatter in the data for individual rabbits. Thus IAA effects on mitosis and aqueous flow resembled the sequelae of x-irradiation qualitatively, but with a somewhat delayed time sequence.

D. Late Lenticular Changes Induced by IAA.—The incidence of IAA-induced lens changes is illustrated by the figures in Table 3. Of the 32 animals subjected to intravenous injections of IAA varying from 20 to 60 mg/kg. body weight, 21 showed lenticular changes in form of (*a*) exaggeration of the sutural opacities, (*b*) vacuolation, and (*c*) formation of granular and diffuse opacities in the posterior cortex, the anterior cortex, and—in later stages—throughout the whole lens.

The appearance of the lenticular changes by slit-lamp examination was strikingly similar to what has been observed in cases of beginning radiation cataract. Best visibility of these alterations was obtained with straight or almost straight incidence of the light beam at peak illumination.

The first noticeable change was an exaggeration of the posterior sutural opacities (Fig. 2), which Poppe [11] considered to be developmental variations. They consisted of

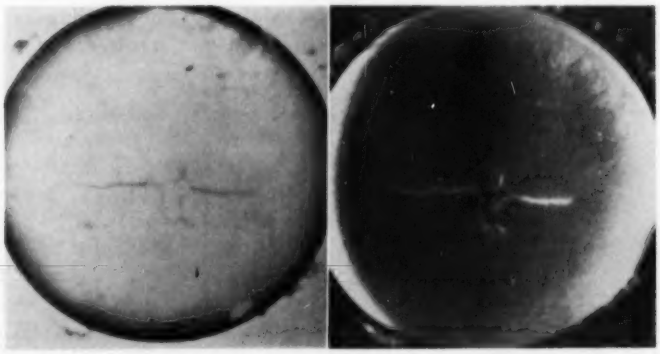


Fig. 2.—Photograph of normal rabbit lens. Sutural opacities at posterior facet. Left, dark-field illumination; right, transillumination.

granular dots situated along the posterior suture lines, impressing the examiner as aggregates of minute vacuoles when observed with transpupillary retroillumination. The histological picture of posterior sutural opacities is shown in Figure 3. Posterior sutural opacities often developed sagittal cataractous connections to the nucleus at the end of the second month or later. Only a significant increase of the preexisting opacities was regarded as positive indication of

Fig. 3.—Photomicrograph of posterior cortex, showing irregularities related to opacities as shown in Figure 1. (Reproduced from Cibis, P. A., and Noell, W. K.: Report 55-45, U. S. A. F. School of Aviation Medicine, Randolph Field, Texas, 1955).

IAA-effect. It was usually found in connection with vacuolization (Fig. 4.)

Vacuole formations were observed in about 65% of the IAA-treated animals after a latent period of one to three months. They developed preferentially in the post-equatorial area, the posterior pole, or at either side. In a few cases they were of transient appearance, developing after one month or two and vanishing in the following three or four weeks. The majority of the recorded

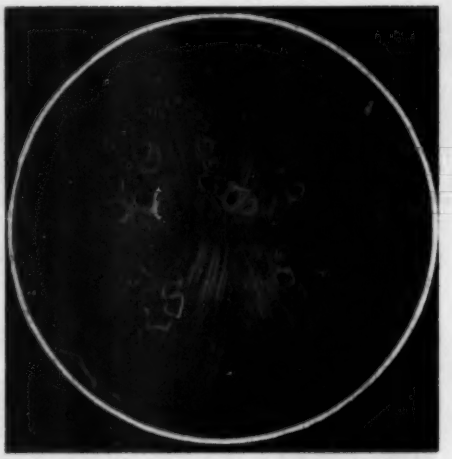
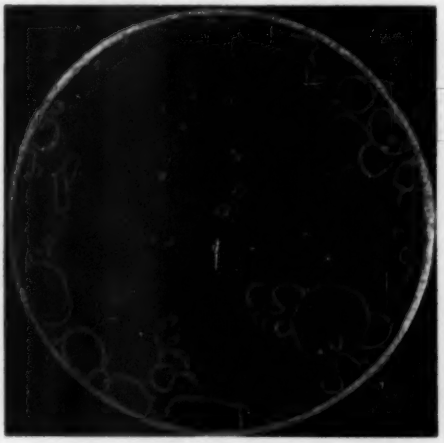


Fig. 4.—Schematic drawing of vacuole formations at posterior pole of rabbit lens, three months after intravenous injection of 40 mg/kg. of IAA.

vacuoles, however, exhibited consistent growth and a tendency to form groups and cluster-like aggregates (Fig. 5). These were preferentially located in the postequatorial zone, where they reached respectable dimensions in three cases.

Figure 6 is a photograph of the same rabbit lens as shown in Figure 5, but it was taken at the time of killing, i. e., seven months after the injection of 40 mg/kg. of IAA. At this stage, the lenticular changes

Fig. 5.—Schematic drawing of vacuole formations in posterior cortex. Rabbit five months after intravenous injection of 40 mg/kg. of IAA.



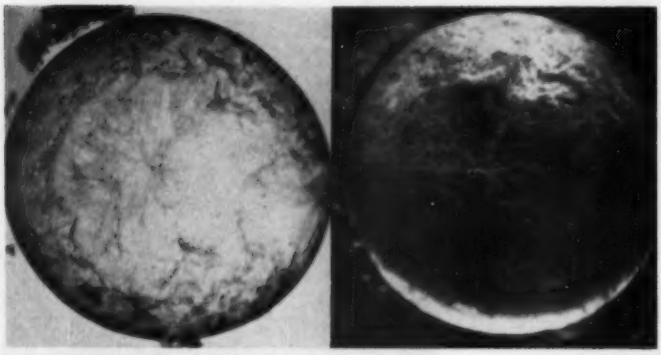


Fig. 6.—Photograph of posterior facet of the same animal, but seven months after administration of IAA. Left, dark-field illumination; right, transillumination.

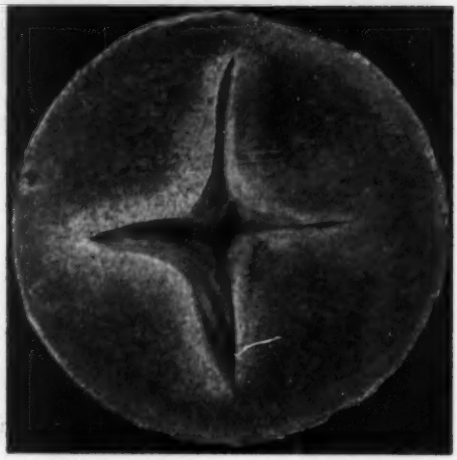


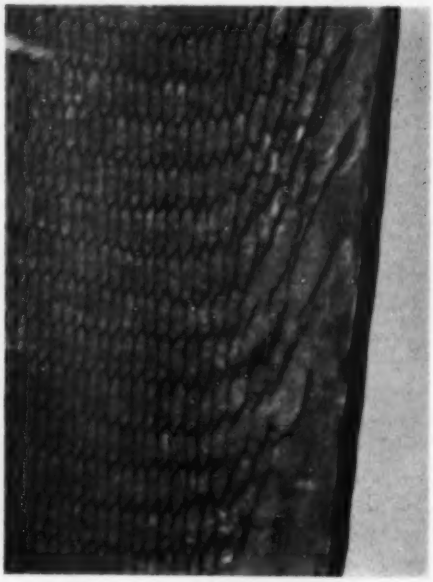
Fig. 7.—Drawing of slit-lamp appearance of lens shown in Figures 3 and 5. Notice sutural and lamellar separation of lens fibers.

closely resembled those described in advanced cases of radiation cataract. They were paired with signs of severe lens fiber swelling. The anterior cortex showed sutural separation and lamellation, as illustrated in Figure 7.

E. Histopathological Findings.—The histologic changes in the early phase of IAA-induced ophthalmopathy were represented by unspecific vascular reactions. Edema of the uveal tissue and congestion of the blood vessels associated with exudation into the anterior and posterior chamber were common findings. In any case of extravasation, erythrocytes dominated the picture.

Chronic changes (two months or longer) involved the corneal endothelium, ciliary body, choroid, retina, and lens. The corneal endothelium revealed cytoplasmic swelling and separated easily during the sectioning and staining procedures. Iris and ciliary body exhibited a tendency to fibrosis and and formation of cysts within the epithelium and stroma of the ciliary processes. The histologic changes in the retina confirmed those described by Noell.[3]

Prime interest was focused on the histopathology of the lens. Significant cataracFig. 8.—Photomicrograph of posterior portion of rabbit lens, four months after administration of IAA (40 mg/kg). Lens fiber swelling and thickening of posterior capsule. Formalin 10%; hematoxylin and eosin.



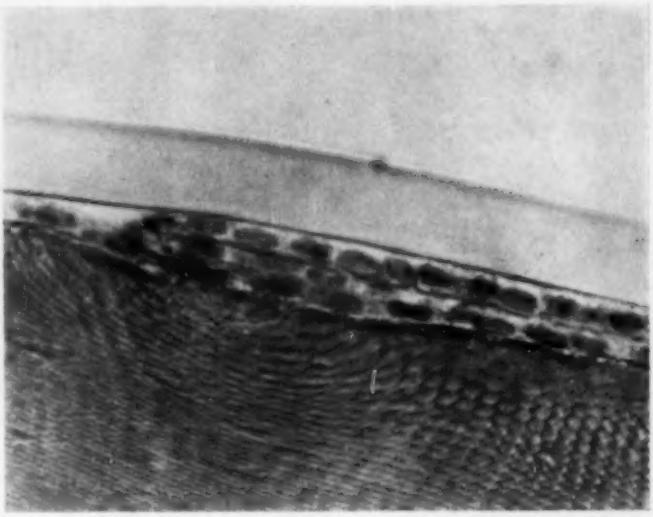


Fig. 9.—Photomicrograph of anterior portion of rabbit lens, four months after intravenous administration of 40 mg/kg. of IAA. Swelling of capsule, proliferation and duplication of epithelium layer, distortion of lens fiber structure. Formalin 10%; hematoxylin and eosin.

tous changes were observed exclusively in lenses of animals killed later than two months after the administration of IAA. The main lesions in these cases were (*a*) thickening of the posterior capsule (Fig. 8); (*b*) swelling of the anterior capsule (Fig. 9); (*c*) proliferation of the epithelial cells in the preequatorial zone and at the equator (Fig. 9); (*d*) displacement of cells into the subcapsular zone of the postequatorial area (Fig. 10); (*e*) degeneration of displaced epithelial cells and faulty lens fiber formation, particularly in the posterior cortex; (*f*) balloon-cell formations (Fig. 12); (*g*) amorphous granular debris and vacuolization (Fig. 13).

The changes in morphology and topography of the epithelial elements in the lens following intravenous injection of IAA are pathognomonic for a disorganized and defective formation of lens fibers. At the anterior pole, epithelium and cortex ap-

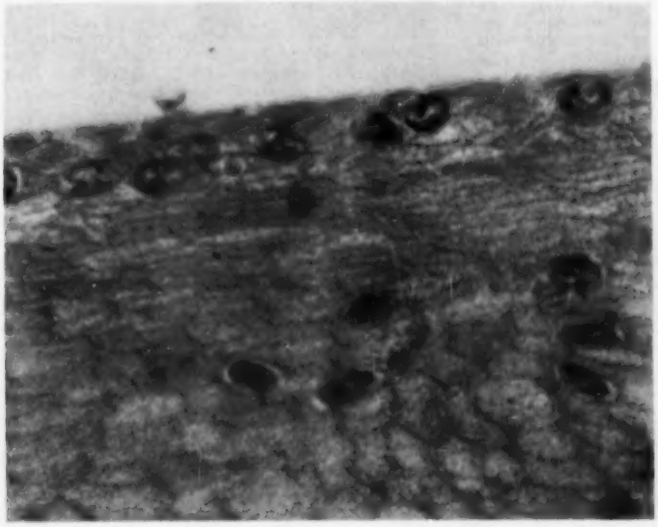


Fig. 10.—Photomicrograph of posterior portion of rabbit lens, three months after intravenous administration of 40 mg/kg. of IAA. Displacement of epithelial cells behind the equator. Capsule artificially separated. Zenker fluid; hematoxylin and eosin.

Fig. 11.—Photomicrograph of posterior portion of rabbit lens, four months after administration of 40 mg/kg. of IAA. Faulty lens fiber formation. Pyknotic nuclei within granular cytoplasma. Formalin 10%; hematoxylin and eosin.

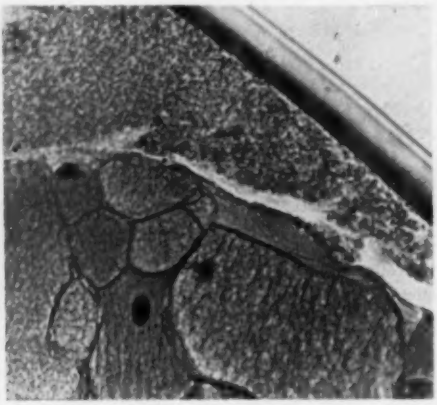


Fig. 12.—Same as in Figure 8. Photomicrograph of balloon cells. Some of them ruptured, resulting in granular debris in subcapsular zone. Formalin 10%; hematoxylin and eosin.

peared least affected. Proliferation of the epithelium resulting in duplication of the epithelial layer in the preequatorial zone was observed once (Fig. 9). This occurred in a lens with advanced changes, in which the cortex was almost completely liquefied (Fig. 14). In this stage of cataractogenesis, the condition approached that of a hypermature cataract.

Piling of cells at the nuclear bow and displacement posteriorward was noted in three cases of longer standing (four to seven months). The displaced cells have certain characteristics in common. They vary in size, shape, and affinity to basic stains, indicating degenerative tendencies. The nuclei in the balloon cells appear pyknotic.

One has to be aware of the fact that the histologic study of lens sections by the techniques currently available is relatively unrevealing of the early cataractous changes (Friedenwald et al.[15]). Artefacts are easily introduced and may prevent recognition of pathologic manifestations. Nevertheless, the

Fig. 13.—Same animal as in Figures 3, 5, and 6. Photomicrograph of posterior cortex with balloon cells and vacuolization. Notice remnants of pyknotic nuclei and fine granular precipitates within vacuoles. Formalin 10%; hematoxylin and eosin.

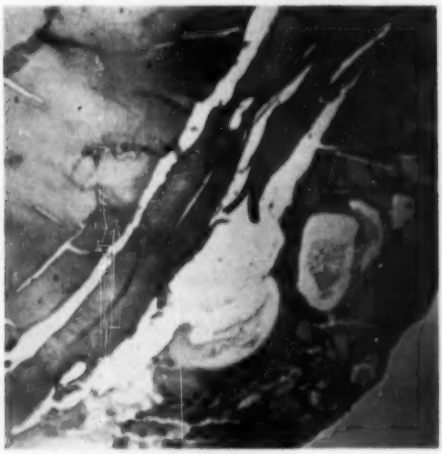
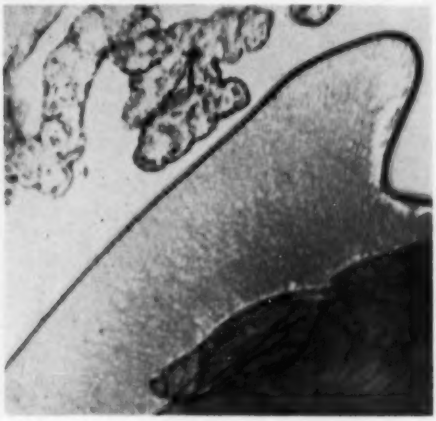


Fig. 14.—Photomicrograph of hypermature cataract in rabbit lens, four months after intravenous administration of 40 mg/kg. of IAA. Formalin 10%; hematoxylin and eosin.



biomicroscopic and histopathologic manifestations of cataractous changes of the iodoacetate-treated rabbit correlate satisfactorily. They are distinguished by the close resemblance to similar changes described in radiation-induced cataract (Leinfelder and Kerr,[18] Rohrschneider,[17] Cogan et al.,[12] von Sallmann et al.,[16,19] Becker et al.[20]) and, therefore, are not pathognomonic for IAA-induced cataract.

Comment

IAA represents a chemical agent which inhibits sulfhydryl-containing enzymes. IAA (Nordmann et al.[9]) as well as ionizing radiation (Barron and his associates[13]) inhibit the glutathione-containing enzyme triosephosphate dehydrogenase, resulting in decreased anaerobic glycolysis. This represents another significant coincidence suggesting that IAA and ionizing radiation may exert their effects over living tissue by the same or closely related mechanisms. A comparison of the IAA- and radiation-induced ocular changes in rabbits is given in Table 4.

With regard to the retina, there is no doubt that one deals with primary effects in the case of IAA as well as of ionizing radiation. In either case the ERG is impaired almost instantaneously, although the histologic changes in form of pyknosis of the rod nuclei and subsequent degeneration of the outer retinal layers require a latent period of several hours in the first, and of days in the latter injury (Noell,[3] Noell et al.[5,7]).

No evidence so far is available that the lens changes observed in IAA-treated animals can be regarded as direct effects of IAA. However, Nordmann and his associates[9] were able to produce lenticular changes in vitro. These in vitro lenticular alterations developed within a few hours and consisted of diffuse opacifications. Such changes have not been observed in vivo, at least not at short time intervals.

The early changes after intravenous injections of 20 to 60 mg. of IAA per kilogram of body weight consisted of exudation into the anterior chamber, the posterior chamber, and the vitreous body; partial suppression of aqueous humor secretion, and inhibition of mitotic activity of lens epithelium. As in radiation cataracts, it is not known whether any of these manifestations represent indispensable precursers of the subsequent lenticular changes.

Confusion exists with regard to some aspects of terminology. The early lenticular changes such as the inhibition of the mitotic activity do not appear to impair vision and are not detectable ordinarily with the biomicroscope. They represent precataract-

TABLE 4.—*Comparison of IAA-* and X-Ray-† Induced Changes in Rabbit Eyes*

Tissue	Pathologic Changes	Latent Period		References
		IAA	X-Rays	
Retina	Impairment of ERG	20 sec.	10 min.	Noell [3,4]
	Pyknosis of rod nuclei	4-6 hr.	4-6 hr.	Noell et al. [5,7] & Cibis et al. [6,10]
	Degeneration of outer retinal layers	10-14 days	10-14 days	Noell et al. [5,7] & Cibis et al. [6,10]
Aqueous humor	Serous exudation	2 days	6 hr.	Brown, D.V.L., [8] von Sallmann, [19] & present observations
	Cellular exudation	2 days	6 hr.	
	Inhibition of secretion	2 days		
Vitreous body	Cellular exudation	4 days	2-4 days	Present observations
Lens (biomicr.)	Exaggeration of sutural opacities	1-2 mo.	1-2 mo.	Cogan et al. [12] & present observations
	Vacuolization	2-4 mo.	1-2 mo.	
	Opacification	3-5 mo.	1-2 mo.	
	Swelling	4-7 mo.	1-2 mo.	
Lens (histol.)	Inhibition of mitosis	2 days	12-24 hr.	
	Proliferation, displacement of epithelium	2-4 mo.	2-4 mo.	Cogan et al. [12] & present observations
	Ballooning of cells, lens fiber swelling	2-4 mo.	2-4 mo.	
	Capsule swelling	2-4 mo.	2-4 mo.	
	Vacuolization	2-4 mo.	2-4 mo.	
	Extensive liquefaction	4-7 mo.	mo.-yr.	

* 40 mg/kg. body weight intravenous injection of the sodium salt.
† 1700 to 20,000 r with reference to retinal changes; 500 to 1500 r with reference to lens changes.

ous rather than cataractous changes, if there exists any relationship between the early and late changes at all. This consideration applies to IAA-induced lenticular changes as well as to those produced by radiation (von Sallmann [16,19]). The term "phakopathy" may be more appropriate; for it includes conditions of the lens without specification of or reference to etiology, morphology, histology, etc. Designations like IAA-induced phakopathy and radiation phakopathy cover both the acute and chronic alterations produced in the lens by these agents.

Although, in general, the data and observations obtained in studies of the ocular changes induced by IAA and ionizing radiation seemed to correlate exceedingly well, there were certain noteworthy differences. First, the exudative manifestations in the anterior chamber occurred significantly earlier after radiation [16,19,20] than after IAA poisoning. Second, the leading cell type in the exudate following radiation was represented by polymorpho- and mononucleocytes, whereas in the exudate of IAA-treated rabbits the erythrocytes were prevalent. Third, differences were found in the time sequence of mitotic inhibition and suppression of aqueous flow. However, some part of the variation might have been caused by the routes of application of the trauma to the animals. In the case of IAA, the animals were injected systemically, whereas their radiation was restricted to the eyes.

Summary

The early and late effects of intravenous sodium iodoacetate upon the blood-aqueous barrier, the rate of aqueous secretion, the mitotic activity of the lens epithelium, and the biomicroscopic and histological structure of the lens were studied in albino rabbits.

The following acute effects were observed: (1) plasmoid, fibrinous, and cellular exudation into the aqueous humor by 2-3 days; (2) cellular exudation into the vitreous body by 5 days; (3) inhibition of mitosis of the lens epithelium with onset by 2 days and recovery by 16 days; (4) partial suppression of aqueous secretion and fall in intraocular pressure by 48 hours, reaching a minimum at 72 hours and recovering after 5 and 7 days.

Lenticular changes were observed biomicroscopically in 21 of 32 animals (65%) one to three months following the injection of IAA. They resembled the lesions observed in radiation cataract.

The histological changes of IAA-induced ophthalmopathy involved the corneal endothelium, ciliary epithelium, retina, and lens. They simulated the sequelae of radiation, particularly with regard to changes observed in the retina and lens.

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Tonometer Calibration

Determination of P_t Formula by Use of Strain Gauge and Recording Potentiometer on Enucleated Normal Human Eyes

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I. Introduction

The Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology has performed a valuable service in arranging for manufacturers to produce tonometers which are uniform in their various weights and measurements and which give consistent readings. These certified instruments have made possible the comparison of readings taken with different tonometers by different persons in different parts of the country. Thus, a scale reading of 3.0 with the 5.5 gm. weight on a Schiøtz certified tonometer taken by Dr. Smith in New York on a given patient is equivalent to the same reading taken on another certified tonometer by Dr. Brown in Chicago on the same patient.

Accurate calibration of tonometers is important for a number of reasons. Since the Schiøtz tonometer uses several weights, it should be possible to detect variations in ocular rigidity clinically and to compensate for them. Tonography depends very definitely on accurate tonometer calibration, including all the factors involved, if the aqueous outflow measurements are to be compared with other methods, such as that of Goldmann.

The conversion of the various scale readings of the tonometer to millimeters of mercury intraocular pressure has required laboratory measurements on enucleated eyes and extensive mathematical analysis. This work was begun by Schiøtz but in recent years has been carried on chiefly by Friedenwald, with assistance from Kronfeld, Grant, and other members of the committee.

The tonometer, of course, does not measure the intraocular pressure directly but only measures how much the cornea is indented by the tonometer plunger. The degree of indentation of the cornea by the plunger is a function of the intraocular pressure, to be sure, but it is also a function of the compliance of the eye-ball and is affected by variations in corneal curvature and by other factors.

When the tonometer is rested on the cornea, the weight of the instrument produces a considerable elevation of intraocular pressure; consequently, during the determination of tension the pressure in the eye is much higher than it was before the tonometer was applied. Since we are mainly interested in the pressure within the undisturbed eye (P_o), it becomes necessary to determine the relationship between this pressure and the pressure while the tonometer is on the eye (P_t). The rise in pressure which the tonometer produces is due to the displacement of a certain volume of intraocular fluid by the tonometer (flattening of the cornea by the foot-plate and indentation of the cornea by the plunger). This fluid cannot immediately escape from the eye, and so it must produce some stretching of the ocular coats (mainly sclera and cornea). If the ocular coats are very compliant, a given change in volume will produce only a small change in pressure.

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Or, conversely, if the ocular coats are more rigid, a given change in volume will produce a larger change in pressure. This property, which relates changes in pressure to changes of volume in the eye, has been called scleral or ocular rigidity. If one wishes to know the relationship between P_o and P_t for a given eye, it is necessary to know what the ocular rigidity is for that eye as well as the volume of fluid displaced by the tonometer.

In calibrating tonometers to give pressure in millimeters of mercury two methods have been used:

(1) *Direct Method.*—In this method an enucleated eye was connected to a saline manometer by means of a cannula passed through the optic nerve into the vitreous. After the intraocular pressure was adjusted by setting the saline reservoir at a predetermined height, a stopcock at the cannula was closed and the tonometer was placed on the cornea and a reading taken. This procedure was repeated throughout the range of pressures for each plunger weight. Since the pressure in the eye was determined before the tonometer was placed on the cornea, this method (closed stopcock method) measured P_o directly.

Schiøtz's original calibration curves were based on closed stopcock measurements, although these measurements were somewhat erratic from eye to eye. Friedenwald felt that the inconsistency of these measurements was due largely to variations in ocular rigidity from eye to eye and to postmortem changes in rigidity. Of perhaps equal importance was the drop in pressure which occurred as soon as the stopcock was closed, due to the outflow of fluid through the normal drainage channels of the eye. During the present study this fall in pressure, which was continuously recorded, was found to be very rapid at higher pressures, so that serious inaccuracies would have been produced by the older method unless the tonometer readings were made immediately after the stopcock was closed.

On the other hand, if the stopcock was left open and the tonometric readings were taken while the eye remained connected to the manometer, the result was a curve of P_t measurements (open stopcock method). Readings taken in this way were not affected by ocular rigidity or outflow but were subject only to mechanical errors of instrumentation and to variations in corneal curvature and resistance of the cornea to deformation. Open stopcock measurements gave much more consistent results than closed stopcock measurements. Schiøtz noted this and used the open stopcock results to develop a parabolic formula which he then applied to the closed stopcock readings to produce his standardization curves. Since the open stopcock formulas did not fit the closed stopcock data at the ends of the scale, he adjusted his curves to fit as accurately as possible between scale readings 3 and 10.

(2) *Indirect Method.*—In Friedenwald's hands the closed stopcock method gave inconsistent results also. Therefore, in his work, which resulted in the calibration scales of 1948 and 1954, closed stopcock measurements did not enter into the calculations at all. Instead, he used what was called the indirect method.

In using this method three things must be determined: (1) open stopcock measurements for all weights throughout the range of pressures with suitable mathematical formulas to fit the experimental data; from this is known the intraocular pressure while the tonometer is resting on the eye (P_t); (2) the ocular rigidity, which relates changes in pressure to changes in volume in the eye; (3) the volume of fluid displaced by the tonometer, which produces the rise in pressure from P_o to P_t. Having all this information at hand for average normal eyes, it is then possible to work backward from P_t and calculate P_o, the pressure in the eye before the tonometer was applied.

This is exactly what Friedenwald did. In the 1948 scale P_t data from Schiøtz's open stopcock measurements were used. The ocular rigidity formula was the semilogarithmic formula which had been previously derived from the work of older experi-

menters. For data on volume of indentation of the cornea Friedenwald made calculations from the assumed shape of the indentation produced by the tonometer. When these data were combined through the corresponding mathematical formulas, the resultant 1948 calibration scale was in close agreement with Schiøtz's 1924 scale, although the method of analysis was different.

After the acceptance of this scale by the committee and its publication, Friedenwald and other members of the committee continued to work on further refinements of the indirect method of tonometer calibration, culminating in the 1954 calibration.* For this scale the same semilogarithmic formula for ocular rigidity was used. However, instead of using formulas for volume of corneal indentation derived by indirect calculation, as in the 1948 scale, the investigators made direct measurements on excised corneas. The anterior segment of the eye was clamped between jaws of a methacrylate (Lucite) clamp, with the cornea exposed in the center. A water-proof chamber which made up the back of the clamp was connected to a manometer and a graduated capillary. After the pressure was set at a desired level, the tonometer was applied and the volume of fluid displaced was measured by the movement of a bubble in the capillary. After measurements were made with the different weights at various pressures, formulas were derived to fit the data. These formulas related P_t to V_c (volume of corneal indentation).

For P_t formulas Friedenwald made a new series of open stopcock measurements on human, pig, cat, and rabbit eyes. He found that these data fitted very well the formula

$$=a+bR$$

where

W=weight of plunger assembly
P_t=pressure while tonometer is on the eye
R=scale reading of tonometer

This formula was derived from the Fick and Maklakow equation:

$$W=P_t A$$

which states that when the tonometer is resting on the cornea the plunger weight (W) is supported by the intraocular pressure (P_t) acting over the area of corneal indentation (A).

When Friedenwald's data were plotted with W/P_t as ordinate and scale reading (R) as abscissa, a straight line resulted which showed no significant variation with different plunger weights. This was taken to indicate that for a given scale reading the area of indentation of the plunger was the same regardless of the plunger load. By use of the method of least squares the coefficients a and b were calculated for each species. Table 1 is Friedenwald's Table with the figures converted to apply to pressures in millimeters of mercury instead of centimeters of saline as in the original.

TABLE 1.—*P_t Coefficients from Friedenwald*

$$\frac{W}{P_t}=a+bR$$

	a	b
Human	0.1146	0.0162
Human (Schiøtz)	0.101	0.01415
Pig	0.101	0.01415
Cat	0.107	0.01227
Rabbit	0.1078	0.01159
Average	0.1065	0.013615
Value chosen	0.107	0.01227

The result of combining these formulas for P_t, V_c, and ocular rigidity was a new scale of P_o for the Schiøtz tonometer. This was accepted by the committee on tonometers in 1954. It is a scale which is close to the Schiøtz calibration of 1908 and gives P_o values about 4 to 5 mm. lower than the 1948 scale.

Since the purpose of this paper is to present new data on P_t measurements, no detailed discussion of ocular rigidity or volume of corneal indentation will be given. However, it is necessary to mention the importance that variations in ocular rigidity may have in tonometry on a given eye. In tonography, also, it has been shown that variations in ocular rigidity may significantly alter the calculations for facility of aqueous outflow.

* See Reference 1 for a detailed account of this work.

If the tension be taken on a given eye with different tonometer plunger weights, the readings of pressure from the conversion tables should be the same for each weight. However, should the ocular rigidity be different from the average normal value on which the calibration scale is based, the readings with different weights will vary. When the rigidity is greater than normal, the pressure will register higher with the heavier weight and vice versa. For each of the calibration scales Friedenwald devised a nomograph and tables for estimating ocular rigidity clinically by taking tensions with different weights. Although it was realized that a single pair of readings might not be accurate, it was hoped that after several pairs of readings were made it would be possible to detect eyes whose ocular rigidity was significantly removed from the average normal.

Unfortunately, it soon became apparent after publication of the 1954 scale that some discrepancies existed in the scale and the accompanying rigidity tables. When estimates were made of the ocular rigidity by paired readings with the 5.5 and 10 gm. weights, for instance, most eyes were found to have a rigidity much greater than normal, tension with the 10 gm. weight often being 3 to 4 mm. Hg higher than with the 5.5 gm. weight.

In 1955 Friedenwald [2] attempted to remove the discrepancies in the 1954 scale by changing some of the constants in the formulas for P_t and V_c to make the scale conform to the average of a large number of paired clinical measurements made by Kronfeld, Ballantine, and Grant and Trotter. These measurements consisted of 1154 paired readings with the 5.5 and 10 gm. weights, 174 readings comparing 5.5 and 7.5 gm. weights, and 208 readings comparing 7.5 and 15 gm. weights. The mean scale reading was determined for each of the various weights. Friedenwald then determined what changes were necessary in the formulas for P_t and V_c to reduce the discrepancies between the weights at the above-mentioned mean scale readings. It was found that this could be done by changing one of the two coefficients (b) in the P_t formula along with changes in one coefficient of the V_c formula for each weight. The coefficients in the P_t formula were still kept the same for all weights. The changes in coefficients, while not based on any further laboratory measurements, at least did not do violence to the previous data. For instance, the value for b in the P_t formula was changed from 0.01227 to 0.0138. By referring to Table 1 it can be seen that the new value is not at all out of line. In fact, if one notes only the coefficients from human eyes, the latter figure can still be considered too small. One reason for not making a greater change in b was the desire to change the P_o values for the 5.5 gm. weight as little as possible, since these seemed fairly accurate.

Friedenwald acknowledged that these formula changes removed the discrepancies in paired readings at the one value only (mean scale reading for each weight). For the 5.5 versus 10 gm. weights these mean values were 5.39 for the 5.5 gm. weight and 10.10 for the 10 gm. weight. For regions of the scale above and below the mean values it was not certain that the discrepancies would be equally well abolished.

The present study was begun quite inadvertently. After strain gauge, recording potentiometer, and associated equipment similar to that of Grant [3] was assembled for the purpose of making aqueous outflow studies on enucleated and animal eyes, it was decided that it would be a good opportunity to determine whether or not the electronic tonometer used in the glaucoma clinic was functioning properly. Eye-bank eyes were used for this purpose. It soon became apparent that the pressures as recorded by the strain gauge did not always agree very closely with either 1948 or 1954 tonometer calibration scales, especially with the heavier weights. Mechanical tonometers were tried, with similar results. It was therefore decided to postpone the outflow studies and pursue the tonometry matter further. P_t data, which the strain gauge

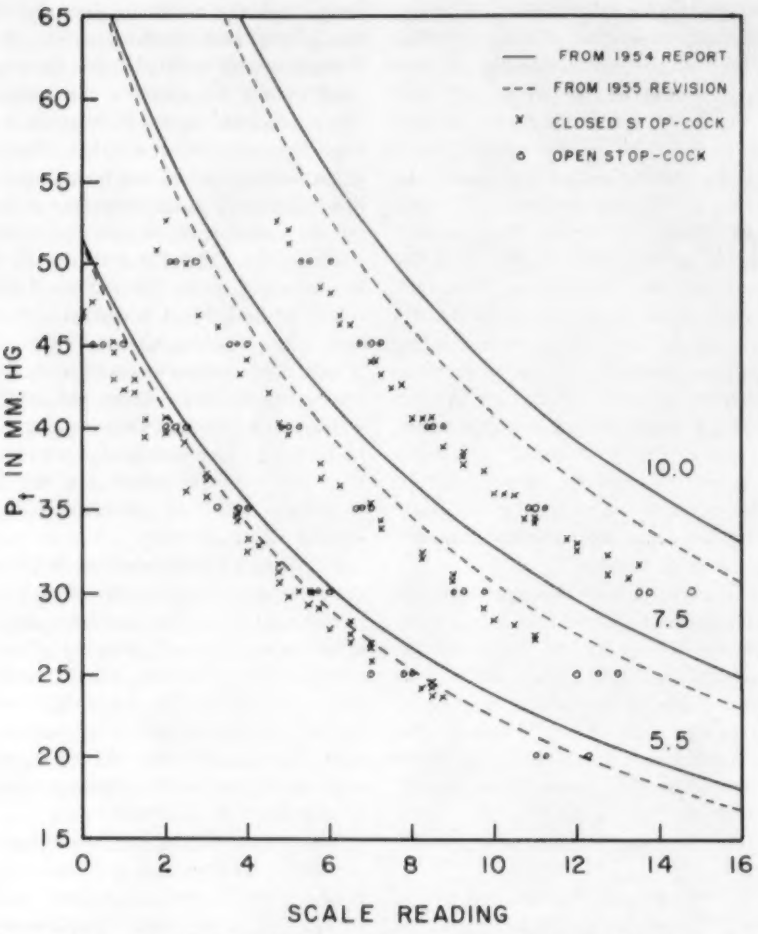

Fig. 1.—Representative P_t readings from the present study plotted with P_t curves from the 1954 Decennial Report by the Committee on Standardization of Tonometers and Friedenwald's 1955 revision. All the readings on Eyes 16 and 17 with Tonometers 1 and 2 are included.

measures simultaneously with P_o, were taken from several eyes and plotted on graph paper with curves from the 1954 P_t formulas. These readings were consistently lower than the 1954 curves. The discrepancy was only slight with the 5.5 gm. weight, but it became greater with each increase in weight (Fig. 1). This seemed to imply that different coefficients were required in the P_t formula for each weight. Curves from the 1955 revision applied to the same chart showed that the discrepancy in the 5.5 gm. weight was largely removed, but only partial correction of the heavier weights was accomplished (if the present measurements are accurate).

Measurements of ocular rigidity were made on the same eyes used for tonometry by injecting known quantities of saline while simultaneously recording the changes in pressure, as described by Grant. When these measurements were repeated on a given eye, the resulting coefficients of ocular rigidity from Friedenwald's formula were found to vary considerably if the initial pressure was altered or if the quantity of

fluid injected was changed. The variations were usually consistent from eye to eye. They consisted of an increase in coefficient of ocular rigidity with decreasing initial pressure and an increase in rigidity coefficient with decreasing volume of fluid injected when the initial pressure was kept constant. The magnitude of these variations was sometimes as great as 100%. Therefore further investigation of the subject of ocular rigidity seemed necessary. This work is continuing along with further work on volume of corneal indentation.

Since the calculations involved in this work are laborious and time-consuming and the P_t measurements are independent of the other measurements, it was decided to publish the data on P_t measurements separately.

II. Methods

Equipment.—Statham pressure transducer (strain gauge) Model P23D with associated power supply; Leeds and Northrup recording potentiometer AZAR (adjustable zero, adjustable range), with range adjustable from 2 to 50 mv.; water manometers calibrated in millimeters of mercury; 22 gauge needle and PE50 polyethylene tubing for connecting eye to strain gauge (0.023 in. (0.058 cm.) inside diameter; 0.038 in. (0.095 cm.) outside diameter); calibrated volume chamber (inverted 5 ml. centrifuge tube with air bubble) connected by three-way stopcock to strain gauge.

The eyes used for this work were normal eye-bank eyes obtained within two to four hours of death and kept under refrigeration in moist containers until used. The total period of time before use was seldom more than 24 hours, never more than 48 hours, after death. Before the experiment was begun, the eye was removed from the refrigerator and placed in a bed of saline-saturated cotton and allowed to warm up to room temperature.

Procedure.—The manometers, with a 250 ml. leveling bulb for a reservoir, and the calibrated volume chamber were connected to one outlet of the strain gauge by means of suitable stopcocks and polyethylene tubing. The 22 gauge needle with hub removed was attached to the other outlet of the strain gauge by 7 in. (17.5 cm.) of PE50 polyethylene tubing.† After the system was carefully filled with isotonic salt solution to eliminate all air except the bubble in the calibrated volume chamber, the chamber was calibrated by weighing the saline discharged when the pressure in the chamber was raised to a certain level and then allowed to return to zero. It was necessary to repeat these weighings at several different pressures in order to develop a curve for the relationship between drop in pressure and volume of saline discharged, because it was found that, especially at higher pressures, this was a nonlinear function.

After calibration of the volume chamber, the eye was then connected to the strain gauge by inserting the needle through the sclera 2 to 3 mm. behind the limbus, through the posterior chamber, between lens and iris, and into the pupil with the bevel directed anteriorly. With the needle in this position the cornea was not visibly distorted, and the iris was lifted off the lens slightly to permit interchange of fluid between anterior and posterior chambers. Without this latter provision the anterior chamber often became very deep when fluid was injected into the eye.

With the apex of the cornea level with the zero point of the system, the recording potentiometer was calibrated against the water manometers by means of the adjustments in the strain gauge power supply and in the recorder itself. This calibration was checked at frequent intervals during the tonometry procedure by connecting the

† A 22 gauge needle was used instead of the 27 gauge needle used by Grant because the greater bore permitted faster exchange of fluid and less danger of the needle's becoming occluded. PE50 polyethylene tubing fits the 22 gauge needle exactly, without the necessity of adapting it with a drop of solder. Also, this tubing, because of its thinner wall, is much more flexible than PE70 tubing and therefore was found to cause very little distortion of the eye.

strain gauge to the successive manometers (adjusted to different pressures) and allowing the pressure to be recorded for a short interval on the paper strip.

The next step was the measuring of ocular rigidity at different initial pressures and with different volumes of fluid injection. At the conclusion of tonometry, and sometimes in the middle of the procedure, the rigidity measurements were repeated.

Tonometry was then done, beginning with the lightest weight. Two certified Schiøtz tonometers (Sklar G51-2418 and G51-2914) and one electronic tonometer (Muller No. 998) were used in this study. These were not specially made instruments, but they were taken to the tonometer testing station at the University of California, where they were weighed and measured carefully. Results are shown in the accompanying table (Table 2). The electronic tonometer was used without an external voltage stabilizer because the available stabilizers introduced inaccuracies into the readings, presumably because of the distorted wave-form which they produced.

The pressure in the eye was raised high enough to register below zero on the tonometer scale by connecting the eye to the saline reservoir at the proper height. The stopcocks were then turned so that only the eye and strain gauge were connected. With the recorder producing a continuous record of the pressure, the tonometer was placed on the cornea and held for 10 to 15 seconds. As the pressure in the eye fell, owing to the outflow of fluid, readings were made at intervals of 3 to 4 mm. Hg from zero scale reading to the lowest pressure to which the eye would fall, usually 4 to 5 mm. Hg. The pressure being recorded at the instant before the tonometer was applied was P_o. The pressure on the chart while the tonometer was resting on the cornea was P_t (Fig. 2). The pressure continued to drop during the time the tonometer was on the eye, owing to the outflow, and this caused a gradual change in the position of the tonometer

TABLE 2.—*Physical Characteristics of Tonometers*

	No. 1 (Sklar G51-2418)		No. 2 Sklar G51-2914)		No. 3 (Mueller No. 998)	
	Load	Weight, Gm.	Load	Weight, Gm.		
Weight of plunger assembly at scale reading 5.0	5.5	5.54	5.5	5.5		
	7.5	7.54	7.5	7.5		
	10.0	10.03	10.0	10.0		
	15.0	15.03	15.0	15.0		
Footplate						
Diameter, mm.	10.0		10.0		10.03	
Curvature	15.0		15.0		15.0	
Diameter of curved surface, mm.	9.5		9.5		9.5	
Plunger						
Diameter, mm.	3.00		3.01		3.01	
Curvature	15.0		15.0		15.0	
Edge curvature	0.25		0.25		0.17	
	Scale Indication					
	Test Block Radius, Mm.	Tonometer Scale	Test Block Radius, Mm.	Tonometer Scale	Test Block Radius, Mm.	Tonometer Scale
	16.0	0.0	16.0	0.0	16.0	0.0
	Micrometer, Mm.	Tonometer Scale	Micrometer, Mm.	Tonometer Scale	Micrometer, Mm.	Tonometer Scale
	0.0	0	0.0	0	0.0	0
					0.1	2.0
	0.25	5.0	0.25	5.0	0.2	4.0
					0.3	6.0
	0.50	10.0	0.50	10.0	0.4	8.0
					0.5	10.2
	0.75	15.0	0.75	15.0	0.6	12.2
					0.7	14.3
	1.00	20.0	1.00	20.0		

Only variations in corneal curvature and resistance to deformation of the cornea pointer, which could be seen if the plunger was working freely. This served as a check that the tonometer was being held properly.

P_t readings could be taken directly from the chart with no corrections for ocular rigidity or loss of fluid to the strain gauge.

should affect them. The P_o readings, however, were not only dependent upon variations in ocular rigidity (which was known for each eye) but were also subject to a small error due to the transfer of fluid from eye to strain gauge and tubing during the rise in pressure which the weight of the tonometer produced. Since the strain gauge required a certain volume of fluid to raise its pressure from P_o to P_t and the polyethylene tubing stretched a little also, some fluid escaped from the eye. The error introduced was small but could be determined accurately and will be included in the calculations of P_o. In the case of the present equipment it amounted to 0.02 cu. mm. saline per millimeter Hg change in pressure for strain gauge and polyethylene tubing together.

A series of 10 to 20 readings was made for each plunger load. At first the pressure was not raised higher than 50 mm. Hg even with the heavier weights, because of the presumed danger of stretching the eye and changing the rigidity. With later eyes the full range of pressures was used.

III. Results

By use of the method of least squares the coefficients a and b were determined in the formula $W/P_t=a+bR$ for each weight. In order to see how well the formula fitted the experimental data, calculated values of P_t were determined for each experimental reading, and the percentage of deviation of the calculated value of P_t from the experimental value was determined. The average deviation for the series was also calculated in the case of each weight, each tonometer, and each eye.

Just how well this formula did fit the experimental data can be seen by inspecting

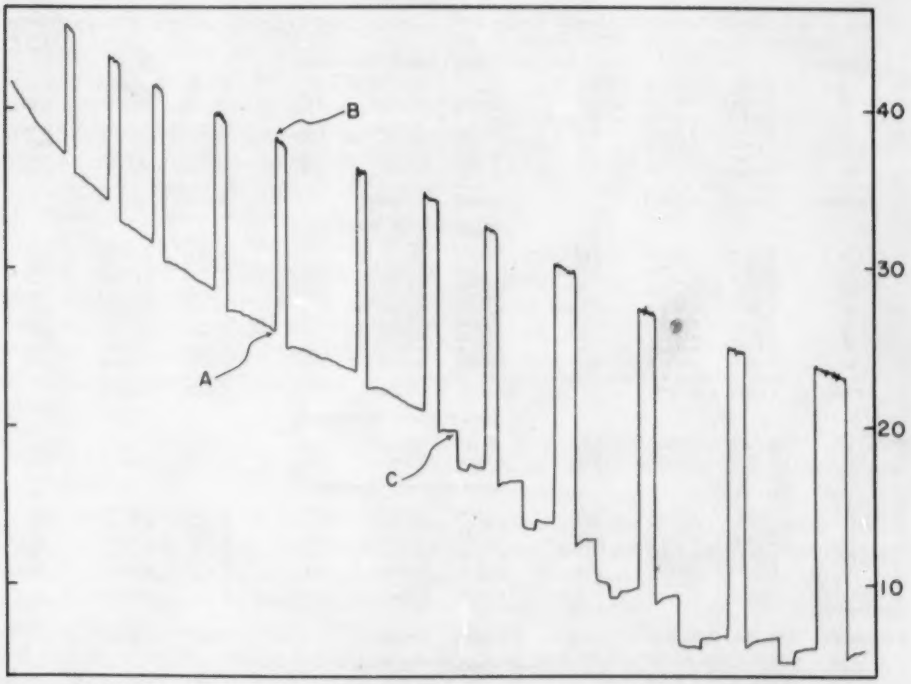

Fig. 2.—Tracing from recorder, showing how tonometer readings are taken. The chart travels from left to right at 1 in. (2.5 cm.) per minute. Point A shows the pressure in the eye at the instant the tonometer is applied. (P_o). Point B is the pressure while the tonometer is resting on the eye (P_t). At Point C the pressure is lowered by connecting the eye to the saline reservoir momentarily.

Table 3. The average deviation was seldom as much as 2% and often was less than 1%. However, the formula $W/P_t = a + bR + cR^2$ should perhaps give a better fit, as pointed out by Friedenwald. Therefore this formula was fitted to the data of several series of measurements. In each case the percentage of deviation was less than with the straight line formula, but the improvement was so slight that nothing was gained by this increase in complexity. In one case the average deviation was improved from 0.93% to 0.85%, and in another, from 1.28% to 0.94%. These were representative.

There are reasons to believe that the method of measuring P_t described above is more accurate than the old open stopcock method. In the first place, conditions are more like those in the living eye, where the weight of the tonometer raises the pressure a considerable amount. In the open stopcock method pressure in the eye was determined by the setting of the manometer, and when the tonometer was put on the cornea it did not raise the pressure but instead forced some fluid out of the eye. Thus, an artificial situation was produced which may have led to inaccuracies, especially when the cannula was placed in the vitreous chamber, where obstruction was more likely to occur. Another possible source of error in the open stopcock method was the fact that measurements were carried to levels of pressure lower than are ever encountered in the living eye in order to cover the full scale of the tonometer. Actually, the intra-

TABLE 3.—*Values Found with the Formula* $W/P_t = a + bR$

Eye	5.5 Gm.			7.5 Gm.			10.0 Gm.		
	a	*b*	Average Dev., %	*a*	*b*	Average Dev., %	*a*	*b*	Average Dev., %
				Closed stopcock, Tonometer 1					
9	0.11136	0.013777	1.94				0.11838	0.015153	1.27
10	0.11297	0.012541	0.93	0.10901	0.015554	1.08	0.12279	0.014869	1.60
11	0.11359	0.014217	0.91						
12	0.11304	0.013986	1.62	0.11620	0.015607	1.09	0.12389	0.015659	1.09
15	0.11682	0.013602	1.27	0.11848	0.014754	1.10	0.12101	0.015498	0.67
16	0.11840	0.012781	1.26	0.12249	0.013731	1.01	0.12279	0.014938	1.12
17	0.11309	0.013398	1.47	0.11291	0.014875	0.74	0.11120	0.016252	0.70
Average	0.11417	0.013480		0.11582	0.014905		0.12001	0.015395	
				Closed stopcock, Tonometer 2					
17	0.10911	0.014156	1.32				0.11417	0.016253	0.64
18	0.11676	0.012088	1.47	0.11881	0.013931	1.45	0.12085	0.014807	1.27
19	0.11782	0.013702	1.03	0.11819	0.015451	1.31	0.12022	0.016637	1.33
20	0.11013	0.012595	1.61	0.11153	0.013769	1.64	0.11393	0.015072	0.83
21	0.10857	0.011808	1.10	0.11677	0.012837	1.52	0.11540	0.015055	0.60
22	0.12479	0.014855	1.29	0.11976	0.018122	1.08	0.12449	0.018731	1.29
23	0.11932	0.010252	0.93	0.12389	0.017667	1.31	0.12997	0.018364	2.12
25	0.11652	0.013502	1.06	0.12016	0.014719	1.20	0.11953	0.016377	0.65
26	0.11066	0.012339	1.62	0.11306	0.013925	1.28	0.11943	0.014248	0.63
Average	0.11489	0.013487		0.11777	0.015053		0.11978	0.016172	
				Open stopcock, Tonometer 1					
16	0.11324	0.013095	2.01	0.11430	0.014106	1.09	0.11324	0.015102	0.96
17	0.10653	0.015050	2.72	0.11378	0.014603	1.13	0.11778	0.015567	0.64
				Open stopcock, Tonometer 2					
17	0.09937	0.015353	2.79	0.10760	0.015826	0.38	0.10909	0.016326	0.56
18	0.10568	0.013711	1.47	0.11294	0.014924	1.07	0.12002	0.014768	1.07
19	0.10866	0.014371	2.29	0.11707	0.014832	0.86	0.11993	0.015767	0.98
20	0.10542	0.012229	1.54	0.11063	0.013463	1.20	0.11255	0.014274	1.08
22	0.11230	0.014496	1.73	0.11677	0.016264	0.61	0.12364	0.016714	1.61
Average of all open stopcock	0.10763	0.014039		0.11330	0.014817		0.11661	0.015503	
Average of all	0.11246	0.013653		0.11572	0.014933		0.11883	0.015747	
				Closed stopcock, Tonometer 3 (electronic)					
5	0.11989	0.011826	0.77				0.11862	0.016001	1.22
8	0.11880	0.011522	1.35	0.11255	0.014175	1.01	0.12724	0.013294	1.60
10	0.11551	0.013282	1.04	0.11618	0.014624	1.37	0.12360	0.015101	1.20
11	0.11492	0.013347	1.84	0.11613	0.015121	0.71	0.11323	0.016536	0.90
Average	0.11728	0.012494		0.11495	0.014640		0.12067	0.015234	

ocular pressure of the living eye (P_o) is probably never less than 8 or 9 mm. Hg, because of the episcleral venous pressure. Enucleated eyes bathed in isotonic salt solution do not fall to pressures much below 5 mm. Hg. When the tonometer is put on an eye with such a low pressure, the resulting pressure (P_t) is almost always over 20 mm. Hg. Open stopcock measurements at pressures of less than 20 mm. are apt to be somewhat erratic and therefore may introduce errors into the calculations affecting the whole scale. Since these lower pressures are not encountered in the living eye (except perhaps after prolonged tonography on a soft eye), it would seem wise to eliminate them from consideration. The present method does this nicely, since P_t measurements are carried down only to the lowest level of P_o.

On some of the same eyes used for strain gauge measurements of P_t, open stopcock measurements were also made for purposes of comparison. This was done by opening the stockcock between strain gauge and saline reservoir and placing the reservoir at the proper height. The pressure in the eye was thus kept constant during tonometry. Readings were taken at intervals of 5 mm. Hg throughout the tonometer scale. Inspection of Table 3 shows that the coefficients derived from these measurements were in good agreement with the strain gauge P_t data, although the readings were somewhat more erratic, resulting in larger deviation of calculated pressures from observed pressures.

IV. Conclusions

The first conclusion to be drawn from these experiments is that the strain gauge method of measuring P_t on enucleated eyes lends further support to Friedenwald's contention that the simple formula, $W/P_t = a + bR$, is an accurate representation of the facts. However, the actual values of the coefficients a and b from the present data do not agree with the figures chosen by Friedenwald, from his measurements on cats' eyes, to be used in the 1954 report. They are in closer agreement with Friedenwald's data from human eyes. This would seem to imply that, in calibrating the tonometer for human eyes, measurements on animal eyes should not be included in the calculations.

Of perhaps greater importance is the fact that these strain-gauge measurements consistently show that for the heavier plunger loads increasingly greater values of a and b are required. This is especially true of b. With use of these coefficients the value of P_t is comparatively lower with the heavier weights than has previously been reported.

As mentioned earlier in this paper, the 1954 tonometer scale tended to give higher tension readings with heavier weights. Friedenwald attempted to reduce these discrepancies between weights by changing the value of b in the P_t formula. Table 4 shows the results of the change adopted by Friedenwald on the clinical measurements previously mentioned. In this 1955 revision, coefficients a and b were the same for all weights, as they had been in the 1954 report. It is interesting to note that when the present values for a and b are used (with larger values for heavier weights) along with the 1954 values for V_c and K_r, the discrepancies in the above clinical measurements are reduced somewhat more than by the change made by Friedenwald in 1955. This is shown in Table 4. It should

TABLE 4.—*Estimated Discrepancies* (ΔP) *for the Paired Clinical Tonometer Readings for Different Values of the Empirical Constants* a *and* b *in the* P_t *Formula,* $W/P_t = +bR$

	Discrepancy in Tonometer Reading, Mm. Hg	
	Plunger Load 5.5 Vs. 10 Gm.	Plunger Load 5.5 Vs. 7.5 Gm.
From 1954 calibration a=0.107 b=0.01227	+3.43	+1.82
From 1955 revision a=0.107 b=0.0138	+1.85	+0.91
From present data a and b different for each weight	+1.33	−0.32

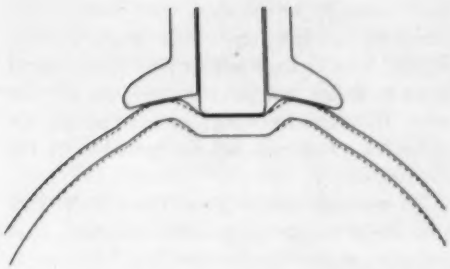

Fig. 3.—Diagram showing how the area of cornea supporting the tonometer plunger is increased with heavier weights when the depth of indentation remains the same. Solid lines represent the situation with a lighter weight. Dotted lines show that with a heavier weight the increased pressure in the eye stretches the cornea and reduces the amount of flattening by the foot-plate. This causes the cornea to pull away from the foot-plate somewhat, and therefore the area of cornea supporting the plunger is increased.

be pointed out that Friedenwald also made changes in the V_c formulas to further reduce these discrepancies. It is not the purpose of this paper to discuss the V_c formulas. This is a subject for future study.

Is it possible to explain why larger coefficients are required for heavier weights in the P_t formula? Figure 3 shows a possible explanation. The quantity $(a+bR)$ in the P_t formula represents the area of the cornea supporting the tonometer plunger (see Fick and Maklakow's equation above). If the coefficients a and b are identical for all weights, this means that for a given scale reading (R) the area of corneal indentation is the same regardless of plunger weight. However, with heavier plunger loads the intraocular pressure must be higher. This means that the ocular volume is somewhat greater and that the sclera and cornea are under more stretch. Since the depth of plunger indentation is the same, the stretching of the cornea would tend to pull it away from the tonometer foot-plate and thus increase the area supporting the plunger. Therefore the heavier the plunger load the greater the area of corneal indentation for a given scale reading. Logically, then, the coefficients a and b should be larger for heavier weights.

Table 5 was prepared by using the average values for a and b from Table 3 taken from all the measurements involving the two Sklar tonometers. The data from the electronic tonometer were not included because of the paucity of measurements with this instrument. Whether the differences in a and b between the electronic and mechanical tonometers represent actual variations in the functioning of these instruments awaits further data. It should be noted also that the curvature of the plunger edge of this particular electronic tonometer is rather sharp, which may significantly alter the results. This is another reason for omitting these readings from the calculations at this time.

The 15 gm. weight has not been included here because of the high pressures which are required to cover the scale of the tonometer when this weight is used. Since measurements of P_o and scleral rigidity were

TABLE 5.—*Intraocular Pressure During Tonometry* (P_t)

Scale Reading	P_t, Mm. Hg		
	Plunger Load 5.5 Gm.	Plunger Load 7.5 Gm.	Plunger Load 10 gm.
0.0	48.91	64.81	84.15
0.5	46.11	60.88	78.93
1.0	43.61	57.41	74.31
1.5	41.37	54.30	70.20
2.0	39.35	51.51	66.52
2.5	37.52	49.00	63.21
3.0	35.85	46.72	60.22
3.5	34.32	44.65	57.49
4.0	32.92	42.75	55.00
4.5	31.63	41.00	52.72
5.0	30.43	39.39	50.61
5.5	29.33	37.91	48.66
6.0	28.30	36.53	46.88
6.5	27.34	35.25	45.21
7.0	26.44	34.05	43.66
7.5	25.60	32.94	42.21
8.0	24.81	31.89	40.85
8.5	24.07	30.91	39.58
9.0	23.37	29.99	38.38
9.5	22.71	29.12	37.25
10.0	22.09	28.30	36.19
10.5	21.50	27.52	35.19
11.0	20.94	26.79	34.24
11.5	20.41	26.09	33.34
12.0	19.91	25.43	32.49
12.5	19.43	24.80	31.68
13.0	18.97	24.21	30.91
13.5	18.53	23.64	30.17
14.0	18.12	23.09	29.47
14.5		22.57	28.81
15.0		22.06	28.17
15.5		21.60	27.56
16.0		21.15	26.97
16.5		20.71	26.41
17.0		20.29	25.87
17.5			25.35
18.0			24.86
18.5			24.38
19.0			23.92
19.5			23.48
20.0			23.05

made as well as measurements of P_t on each eye, it was felt that the relatively unimportant 15 gm. weight should be left out in order to avoid stretching the eyes and perhaps altering the ocular rigidity. When the 15 gm. weight was used on a few eyes, however, the values for the coefficients a and b in the P_t formula were greater with this weight than with the lighter weights, following the general trend of the other measurements. The discrepancy between the 7.5 and 15 gm. weights which appeared in the 1954 scale amounted to +2.40 mm. Hg in Kronfeld's clinical readings with these two weights. The change which Friedenwald made in coefficient b in the 1955 revision reduced the discrepancy to −0.15 mm. Hg. With use of the present data from only three eyes for the 15 gm. weight, the discrepancy is +0.22. These figures are not included in Table 4 because of the relatively few measurements with the 15 gm. weight, but they are mentioned here as further evidence that the strain gauge measurements of P_t tend to fit in with clinical tonometer readings.

It has been found that when tonographic calculations are made with use of the formulas from the 1954 calibration the estimate of the facility of aqueous outflow of the same eye reached by tonography with two different plunger loads tends to be smaller with the heavier plunger load. When P_t values from the present data are used to calculate facility of outflow, this discrepancy between weights tends to be diminished. How much, it is not possible to say.

V. Summary

The work of the Committee on the Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology on the calibration of tonometers is briefly reviewed.

The strain gauge method of calibrating tonometers, devised by Grant, is explained.

The results of more than 1200 individual strain gauge measurements of P_t (pressure while the tonometer is on the eye) on enucleated normal human eyes are given. These results support Friedenwald's contention that the simple formula, $W/P_t = a + bR$, accurately represents the facts. However, the actual values of the coefficients a and b from the present data are somewhat higher than those chosen by Friedenwald. Of greater importance is the fact that increased values of a and b are required with each successively higher plunger weight. The possible mechanism of this finding is explained.

Discrepancies in the 1954 calibration scale are largely removed by using coefficients in the P_t formula from the present data without changing the V_e or rigidity formulas. Further work is necessary before it can be decided whether or not the latter formulas are in need of revision.

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Frequency of Genetic Transmission of Sporadic Retinoblastoma

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The inheritability of retinoblastoma is a matter of practical concern to the patient and to the physician. In many cases, transmission follows the law of simple Mendelian dominance, and approximately 50% of the offspring of an affected person may be expected to have the disease. In the sporadic cases, that is, in cases of retinoblastoma which appear to occur without preexisting retinoblastoma in the family, the manner of transmission is not so obvious. Yet this information is essential to advise these persons concerning the chances of their offspring having the disease.

This information can be obtained only by analyzing the records of patients with sporadic cases who have had children. Such is the aim of this study. Literature regarding the offspring of patients with carefully documented sporadic cases has been scanty.

Hemmes [1] reported in 1931 four patients with sporadic retinoblastoma with a total of nine offspring, none affected with retinoblastoma (see Figure 1, Kindreds 1, 2, 3, 4). He did not report the individual pedigrees, but he said that their families were free of the disease. He concluded that such patients need not be advised against childbearing. Similarly, Herm and Heath [2] reported, in 1956, seven patients with apparently sporadic cases who had had children, only one of whom had borne affected offspring at that time. On the other hand, Lange [3] reported a sporadic case in which the patient transmitted bilateral disease to one of his four children (see Figure 1, Kindred 5). And Reese [4] said, in 1956, that he had seen only one survivor of the disease who had healthy children (three children), inferring that the likelihood of transmissibility was high. It should be noted, however, that all but one of Reese's families were ascertained through an affected child.

The present study was undertaken to determine the incidence of retinoblastoma among the offspring of sporadic cases who had been treated at the Massachusetts Eye and Ear Infirmary. Most of these cases had been included in the series of Herm and Heath, but the lapse of three years at this critical period has permitted more extensive documentation. It was also necessary to obtain more complete information on the past genealogy of these patients to confirm that the cases were, in fact, sporadic.

The method of this investigation was to contact all survivors of retinoblastoma, age 19 or older, pathologic specimens from whom had been studied at the Massachusetts Eye and Ear Infirmary. Detailed family histories for three generations were requested from those who have children, this being the maximum amount of reasonably reliable information that was considered obtainable by this method.

Results

A total of nine adult survivors with children were located. So far as could be determined, eight of the nine represent sporadic occurrences (Kindreds 6 to 13). Two of these patients have transmitted retinoblastoma to two of their three chil-

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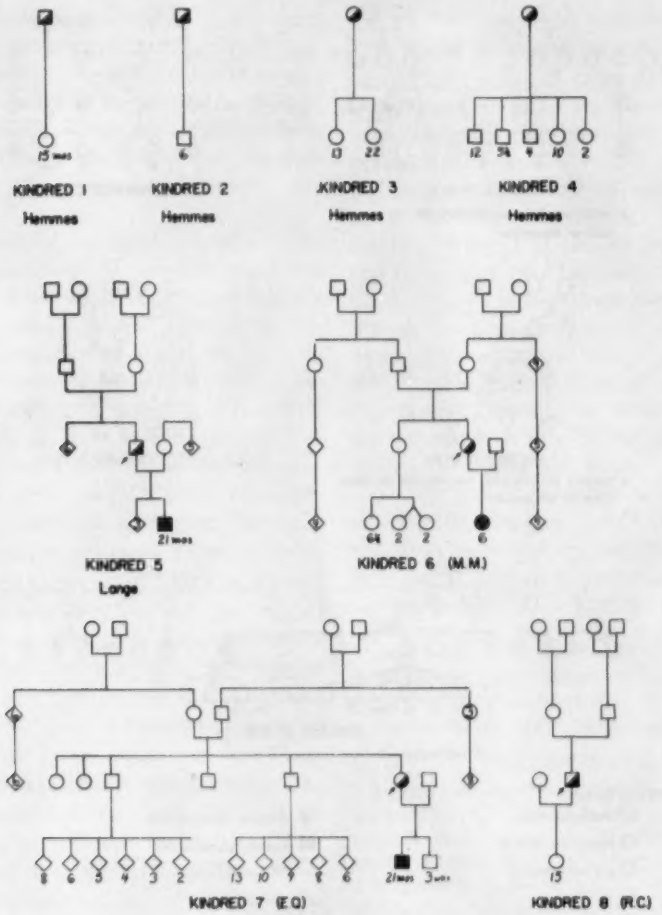

Figure 1

dren (Kindreds 6 and 7). The other 6 adults have a total of 15 apparently healthy children, 12 of whom are over 3 years of age. Eighty-seven per cent of affected patients are recognized by the age of 3 (Jain, 1950 [5]); hence, few of the children past the age of 3 may be expected to develop retinoblastoma.

In summary, the data show that 8 patients, who represent isolated instances of retinoblastoma, have had 18 children, 13 of whom are age 3 or older. Two, one of whom is only 1¾ years old, have developed retinoblastoma.

Comment

In the present investigation there are 13 children past 3 years of age descended from affected persons who appear to be isolated cases in their families. These children may be considered to have passed the period of risk for developing retinoblastoma. There is, in addition, one child less than 3 years old who is affected, who therefore may also be considered to have completed the period of uncertainty. Thus, 14 children have passed the period of risk. Two of these fourteen children are affected. Seven would be expected on the basis of dominant

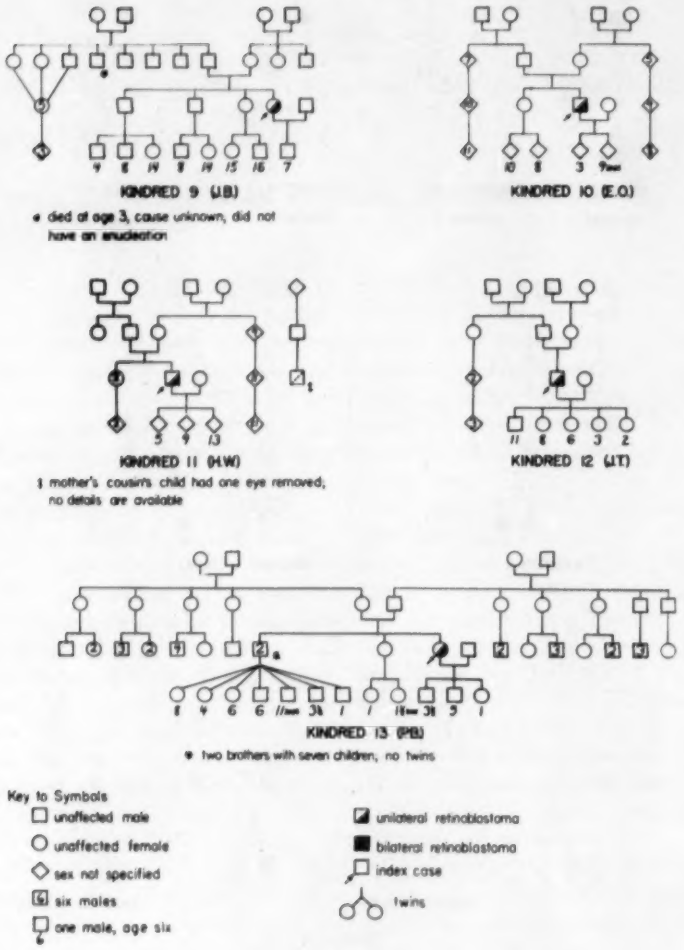

Figure 2

inheritance with complete penetrance. Penetrance, however, is known to be incomplete. It has been estimated by various authors to range from about 80% to over 95% (Franceschetti and Bischler, 1946[6]; Falls and Neel, 1951[7]). If penetrance is indeed as low as 80%, the expected number of affected children is 5.6. The probability that the sample may have been drawn from such a population is approximately 5%. If it is as high as 95%, the probability falls to less than 2%.

Inclusion of the seven children past the age of 3 years in the less well documented pedigrees of Hemmes (Pedigrees 1 to 4) and the four children in Lange's pedigree (Pedigree 5) provides a total of 25 children descended from affected parents who appear to be isolated cases. Only 3 of the 25 are affected, whereas 12.5 would be expected on the basis of complete penetrance and 10 would be expected on the basis of 80% penetrance. If one assumes 80% penetrance, $\chi_1^2 = 10.667$; $P < 0.01$.

The analysis suggests that fewer than 40% of the offspring of patients with sporadic cases of retinoblastoma develop this disease. Inclusion of the unaffected children less than 3 years of age, by weighting them according to the proportion of the risk they had passed, would serve to reinforce this suggestion.

This finding, if confirmed, would require the reconsideration of several questions, such as the following: Is all retinoblastoma due to the same dominant gene, with isolated cases representing mutations? If so, why is penetrance so much lower among the offspring of isolated cases than it is among the offspring of those which are not isolated? Alternately, is retinoblastoma due to dominant genes at more than one locus, with one or more of these genes having a greatly reduced penetrance? Is one or more of these genes recessive? May a portion (perhaps a large portion) of the isolated cases be phenocopies (i. e., environmentally induced copies of genetically determined characters) and therefore not transmissible?

Vogel, 1954,* from a consideration of the proportion of cases which are hereditary and the relative fertility of retinoblastoma patients, concluded that only 25% of all sporadic cases represent mutations. Our findings tend to support his conclusions.

These considerations are of importance in problems concerned with estimating gene frequency and mutation rates, and until they are answered such estimates must be considered tentative. The answers to the questions in the preceding paragraphs are of importance in determining the advice to be given concerning the probability of a recurrence of the disease in the descendants of affected persons. Only more extensive data can provide satisfactory answers to these questions. Apparently no single center can collect enough data by itself. It is urgent, therefore, that many centers collect similar data and publish them in detail to permit an analysis to be made on the combined data.

Summary and Conclusions

In order to determine the inheritability of so-called sporadic cases of retinoblastoma, the pedigrees of eight new cases have been analyzed and compared with those previously reported. These 8 patients have had a total of 13 children over 3 years of age at the time of reporting. Retinoblastoma has occurred in two of these children, one in each of two families. On the other hand, 6 of these 8 patients have not transmitted the disease to any of their 15 children, 12 of whom are over 3 years of age. The data indicate that the disease involves significantly fewer than 40% to 50% of the offspring, which is the expected frequency in nonsporadic cases.

To the patient who has a sporadic case of retinoblastoma, it would seem fair to say, until more data are available, that there is a one in four chance of transmitting the disease to 40% to 50% of his progeny.

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Retinitis Pigmentosa with Normal Electroretinogram

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The case of a 17-year-old Negro youth who exhibited classical clinical retinitis pigmentosa but showed an eletroretinogram (ERG) of normal response and contour is here reported.

The most striking changes in the ERG are found in retinitis pigmentosa,[1-3] the response of the retina being totally absent or extinguished even in the early stages of development. A few subnormal ERG's have been described in retinitis pigmentosa,[4] but these were elicited only under favorable conditions. In congenital nyctalopia only the photopic, or cone, components are apparent.[5]

Report of a Case

The only significant items in the patient's history were difficulty with night vision and somewhat less difficulty with day vision. The patient's two sisters have normal vision. Neither the father nor the mother are affected. Neither of the parents had any siblings. The patient's maternal grandfather has had night blindness all his life, and the grandfather's grandmother had poor vision of unknown cause most of her life.

The clinical ocular findings of note were (1) a rather marked compound hyperopic astigmatism; (2) fundi with waxy discs (Figs. 1 to 4), attenuated arterioles, and pigmentary disturbance in the midperiphery, and (3) visual fields demonstrating bilateral ring scotomata of approximately equal shape (Fig. 5). The fundus changes were interpreted by several ophthalmologists as being typical of retinitis pigmentosa. Multiple ERG's were taken, with similar results.*

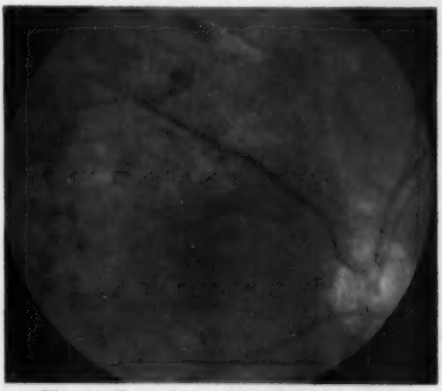

Fig. 1.—Posterior pole of disc, right eye.

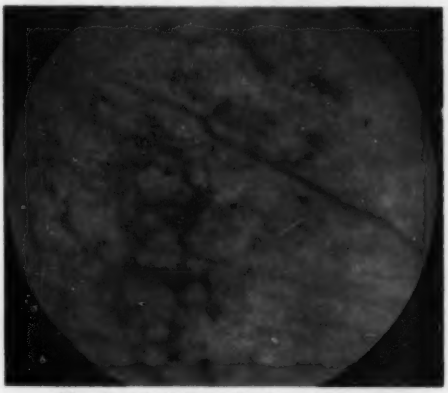

Fig. 2.—Periphery, fundus, right eye.

Method and Results of ERG Studies

Electroretinograms were recorded with a contact lens electrode with a Grass electro-

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Walter Reed Army Medical Center: Ophthalmology Service, Walter Reed Army Hospital (Lieut. Col. Skeehan); Ocular Research Unit, Walter Reed Army Hospital (Lieut. Col. Passmore); Walter Reed Army Institute of Research (Dr. Armington).

*Three tracings on separate dates were performed at the Walter Reed Army Institute of Research, and a fourth, at the National Institute of Health.

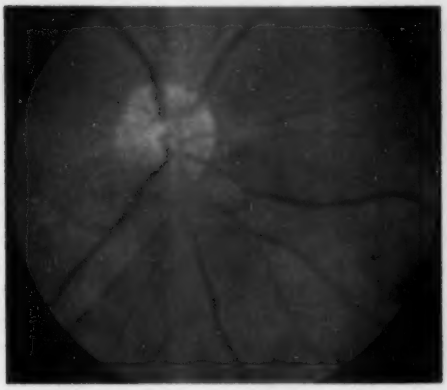

Fig. 3.—Posterior pole of disc, left eye.

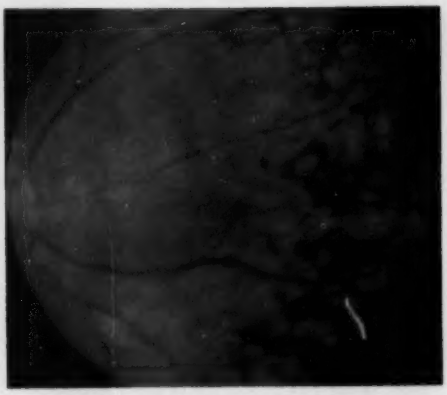

Fig. 4.—Periphery, fundus, left eye.

encephalograph apparatus. They were elicited with a Grass photostimulator. Tracings were obtained immediately after the patient entered the recording booth and at intervals during an ensuing 30-minute period of dark adaptation. For comparison, a series of recordings were obtained from a normal eye under identical recording conditions.

The patient's electroretinograms are shown in Figure 6. By comparing them with those of the normal eye it will be apparent that the ERG, although small, is of charac-

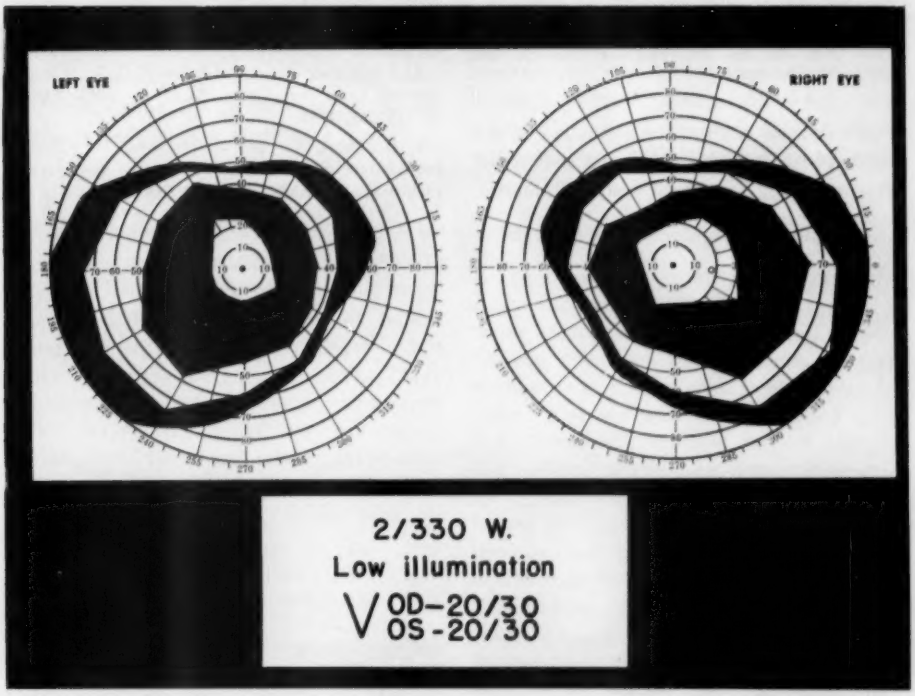

Figure 5

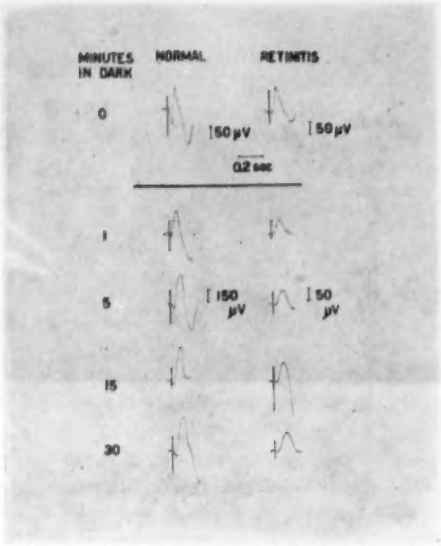

Fig. 6.—Comparison of ERG records of patient with retinitis pigmentosa and those of a normal eye. The upper two tracings were obtained with the same gain and with the eye light-adapted. The test flash used for the normal eye was 0.6 log units below that for the abnormal. Lower tracings were obtained during the course of dark adaptation with test flashes of the same luminance, but with a higher gain for the abnormal eye. Vertical line marks stimulus onset.

teristic normal contour. An A-wave is not clearly present in the responses shown but came in strongly at high test flash luminances. During dark adaptation, the ERG of the patient as well as that of the normal eye underwent a progressive increase in size. Except for its reduced amplitude, this ERG showed no abnormal features.

Comment

Although this patient's ERG indicated some abnormality, the response was much greater than has normally been found in cases of retinitis pigmentosa. The ERG, then, cannot be relied upon to verify unerringly the diagnosis of retinitis pigmentosa.

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Retinitis Pigmentosa

A Histopathologic Study with a New Technique

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Primary pigmentary degeneration of the retina is considered a heredodegenerative disease of the eye. It typically involves both eyes, begins in the region of the equator, and proceeds posteriorly. The present knowledge of the pathology of this clinical entity is composed of the findings of a large number of investigators (Landolt,[1] Wagenmann,[2] Lister,[3] Stock,[4] Leber,[5] Ginsberg,[6] Gonin,[7] Suganumba,[8] Verhoeff,[9] Ascher,[10] Cogan,[11] among others). The main findings of these authors are very adequately summarized in the textbooks of Duke-Elder,[12] Friedenwald,[13] and Elwyn.[14]

The present paper is a report of some new pathologic details which were observed histologically in the eyes of an advanced case of primary pigmentary degeneration, which were stained with the silver carbonate techniques of del Rio Hortega.

Report of Case

A male patient was first seen in 1928 by Dr. F. B. Fralick, chairman of the Department of Ophthalmology of this University. Dr. Fralick made the diagnosis of typical bilateral primary pigmentary degeneration of the retina (retinitis pigmentosa). There were bilaterally night-blindness, "gun-barrel field," bone-corpuscle-like pigment degeneration of the peripheral retina, waxy pallor of the optic disk, and narrowing of the retinal arteries and veins. At the next examination, in 1937, Dr. Fralick found a beginning cortical cataract. In 1938, the patient was admitted to the Ypsilanti State Hospital with a diagnosis of senile dementia and was virtually blind. The pedigree of the family of this patient as studied by the Heredity Clinic of this University revealed two more members of the family to be affected with primary pigmentary degeneration (Fig. 1). The mode of heredity transmission might be that of the recessive sex-linked type. However, the knowledge of the family is too limited for a final decision.

The patient died at the age of 75 years on May 14, 1955, in the Ypsilanti State Hospital. At postmortem examination, Dr. K. Scharenberg, of the Neuropathologic Institute of the University of Michigan Hospital, found "nonspecific senile brain changes" only. Both eyes of the patient were obtained for histopathologic examination.

Method of Pathologic Examination

The eyes were removed 15 hours after death and immediately fixed in brom formalin (Cajal solution). One half of each eye was embedded in paraffin, cut in serial sections, and stained with hematoxylin and eosin. Flat sections of the isolated retina and choroid of the other half of each eye and sections of the optic nerves were made on the freezing microtome. The silver carbonate techniques of del Rio Hortega were used to stain these sections. The techniques of Hortega have been further developed by Scharenberg (see Scharenberg and Zeman[15]) and have proved to be very useful in demonstrating histologic details of human retina, choroid, and optic nerve under normal and pathologic conditions (Wolter,

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Goldsmith, and Phillips[16]; Wolter[17-25]; Wolter and Liss[26]; Liss[27]).

All illustrations in this paper except Figures 1 and 2 are unretouched photomicrographs.

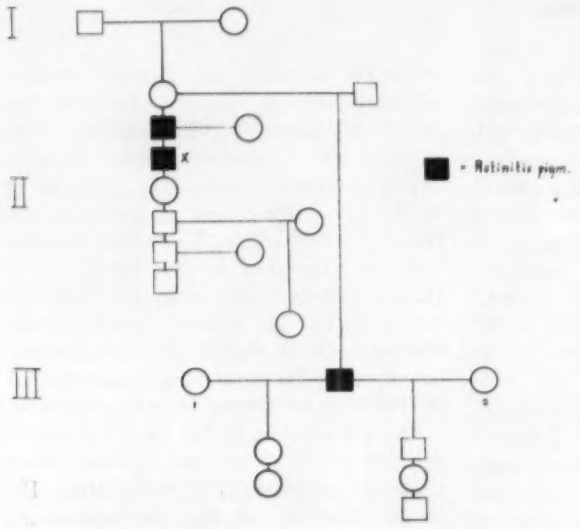


Fig. 1.—Pedigree of the family of the patient. Generations are indicated by Roman numerals. Only males were affected, and transmission of the disease took place through an unaffected female. X indicates the patient the eyes of whom were studied in the present paper.

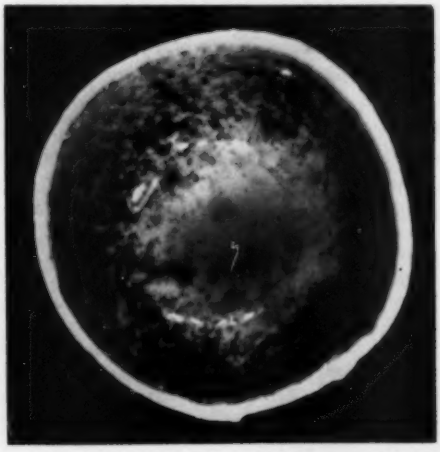
Pathologic Description

Macroscopic Findings. — The size and shape of the eyes were normal. There were bilaterally advanced cataracts, and the vitreous was liquified. Both peripheral retinae showed extensive "bone corpuscle formation" of dark-brown pigment (Fig. 2). Retina and choroid were intimately connected and could not be separated in either eye. These layers were distinctly thinner, and the retinae were much denser in consistency than that of a normal human eye.

Microscopic Findings. — Very advanced histological changes of the retina, choroid, and optic nerve were observed in both eyes. These changes were composed of reaction, degeneration, or scarification of the following tissue systems: (1) the pigment epithelium of the retina, (2) the blood vessels of retina and choroid, (3) the neuroglia and the perivascular glia of the retina, (4) the neurons of the retina, and (5) the optic papilla and the optic nerve. The changes in the two eyes of this patient were so similar that it seems reasonable to discuss both eyes simultaneously.

1. Changes of the Pigment Epithelium of the Retina: In the peripheral retina, the honeycombed cells of the pigment epithelium had completely disappeared from the normal site between the choriocapillaris (Bruch's membrane) and the retina. Only scattered pigment granules remained of these cells.

Fig. 2.—Photograph of the posterior half of the left eye of the patient. The liquefied vitreous has been removed. There is extensive "bone corpuscle formation" in the retina.



Pigment was irregularly distributed all through the inner layers of the scarified retina. It was especially concentrated around the small blood vessels (Fig. 3). Horizontal sections of these inner layers of the peripheral retina revealed an extensive pigment sheathing of all the blood vessels. Many of these vessels showed degenerative hyalinization and occlusion (Fig. 5) or had disappeared completely. In the latter situation, the arrangement of the remaining pigment granules still indicated the course

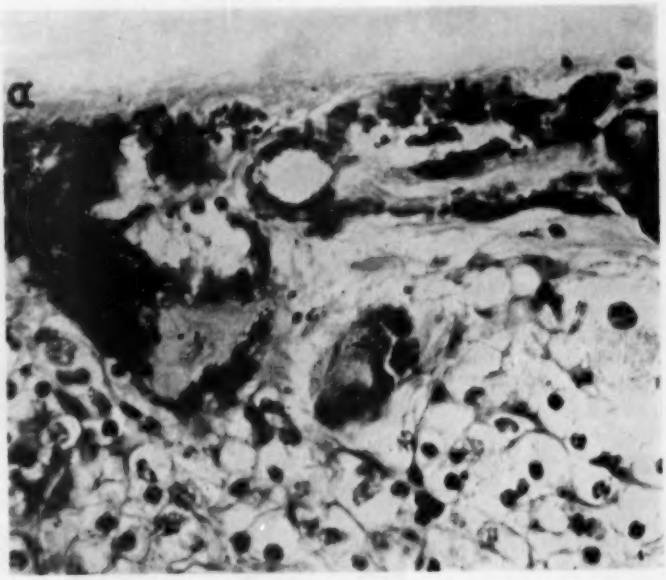


Fig. 3.—Deposition of pigment around blood vessels of the inner retinal layers. (*a*) Inner limiting membrane. Photomicrograph; hematoxylin and eosin; × 300.

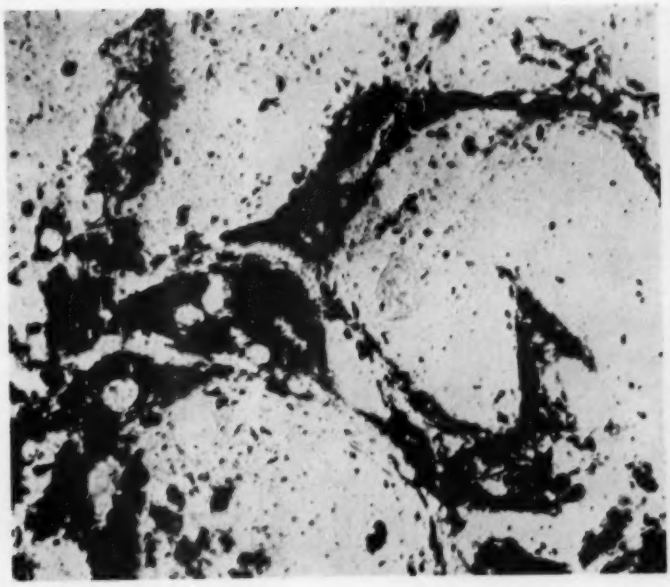


Fig. 4.—Horizontal section through inner layers of peripheral retina. The arrangement of remaining pigment indicates the course of degenerated blood vessels. There is also diffuse deposition of pigment in the retinal tissues. Photomicrograph; del Rio Hortega method; × 300.

of the degenerated blood vessels (Fig. 4). Besides the localized concentration of large amounts of pigment around blood vessels, there was also diffuse deposition in glia cells and there were pigment-epithelium-like cells, containing large amounts of pigment, all through the peripheral retina.

In the central area of the retina, patches of normally arranged pigment epithelium survived (Fig. 6). The pigment cells in these patches were somewhat irregular in size, and some of them contained lipid substance and very little pigment. Except for these patches of pigment epithelium in the

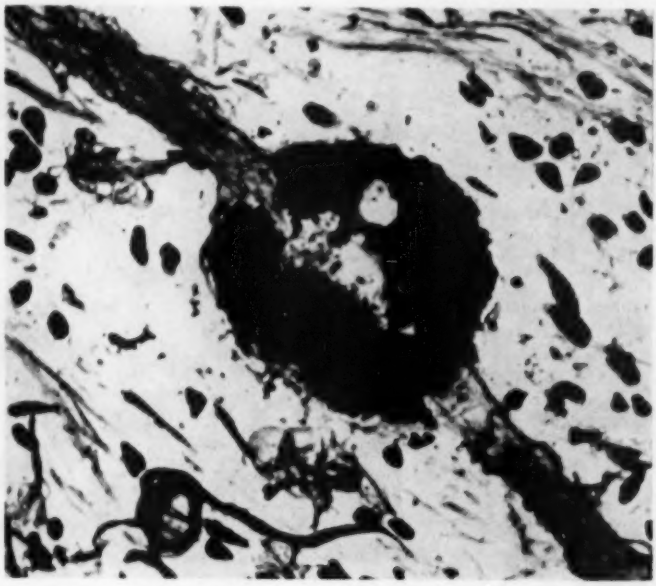


Fig. 5.—Small retinal blood vessel which exhibits obliterative hyaline degeneration and a localized cuff of pigment. Photomicrograph; del Rio Hortega method; × 600.

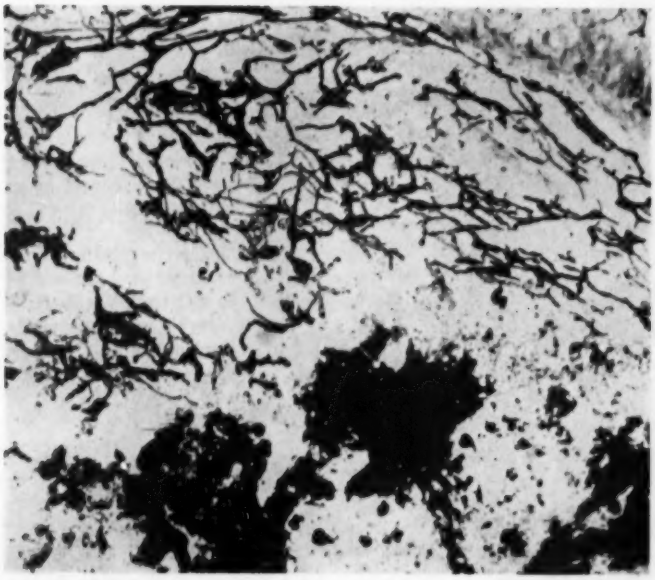


Fig. 6.—Transitional section from central retina into central choroid; only the pigment of the pigment epithelium and of the melanoblasts is stained. Lower half of picture shows irregular patches of normally arranged pigment epithelium. Upper half shows hypertrophic melanoblasts of the choroid. Photomicrograph, del Rio Hortega method; × 150.

central retina, there was direct contact between the mesodermal tissues of the choroid and the neuroectodermal structures of the retina. A wall-like intertwined zone of hypertrophic astrocytes appeared in all areas of such direct contact following the destruction of the pigment epithelium (see Wolter,[20] Fig. 11).

2. Changes of the Blood Vessels in Retina and Choroid: Coarse pigment cuffs, hyalinization, occlusion, and complete atrophy of the small retinal vessels have already been described. All stages of this degenerative process were seen in different areas of the retina. There were only a few normal vessels. Many vessels showed deposition of

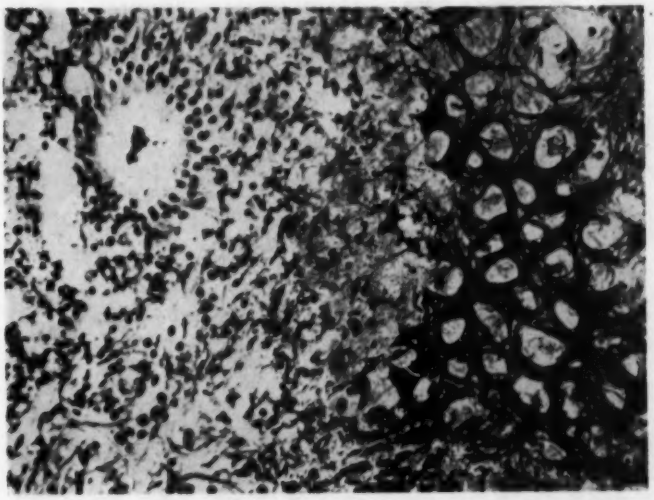


Fig. 7.—Transitional section from central retina into central choriocapillaris. Left half of picture shows faintly stained retinal rosette (see Fig. 9). Right half shows the completely hyalinized choriocapillaris (see Fig. 8). Photomicrograph; del Rio Hortega method; × 150.

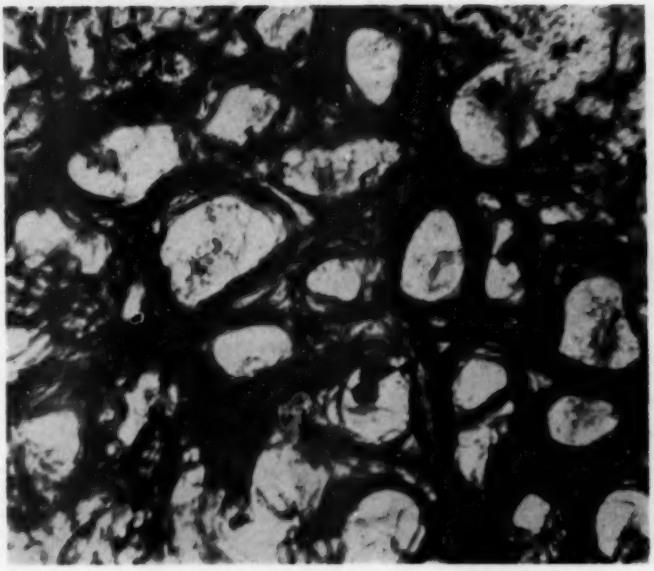


Fig. 8.—Horizontal section of the completely hyalinized choriocapillaris which was preserved as a network of necrotic hyalinized strands without lumen. Photomicrograph; del Rio Hortega method; × 700.

hyaline in their wall but still had a lumen; others were completely hyalinized and remained in the tissue as solid hyaline structures without any lumen at all (Fig. 5). The final stage of this degeneration was a complete dissolution of all vascular remnants. Only the remaining perivascular pigment deposits (Fig. 4) or the surviving perivascular glia (Fig. 13) indicated the site of the degenerated vascular network.

The complete hyalinization of large, continuous areas of the central choriocapillaris of both eyes was an outstanding finding in this study (Figs. 7 and 8). In these areas, the normally delicate capillary vessels were transformed into solid strands of hyaline

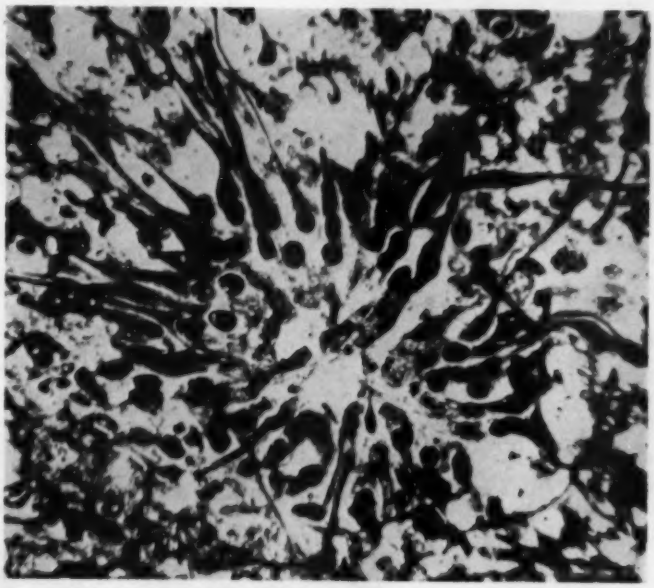


Fig. 9.—Horizontal section through scarified outer layers of central retina. Rosette formation of cylindric cells with long glia-fiber-like processes. Photomicrograph; del Rio Hortega method; × 600.

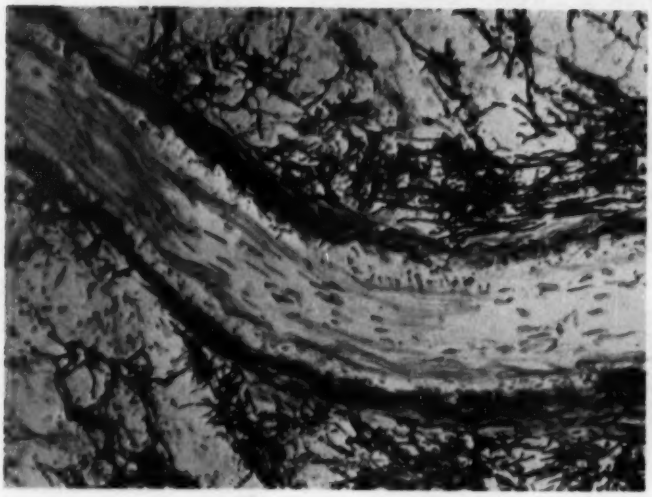


Fig. 10.—Larger artery of the choroid which is surrounded by melanoblasts. The wall of this blood vessel shows only slight fibrosis and hyalinization. Photomicrograph; del Rio Hortega method; × 150.

which had no lumen, contained no erythrocytes, and showed only necrotic cellular remnants of the vessel wall. In more peripheral areas of the retina nothing remained of the choriocapillaris at all.

The larger blood vessels of retina and choroid, especially the arteries, exhibited extensive hyalinization and fibrosis but always had a lumen and were filled with erythrocytes (Fig. 10).

3. Changes of the Neuroglia and the Perivascular Glia of the Retina: The normal pattern of the retinal layers was almost completely lost in most of the retina, especially in the more peripheral areas. Retinal astroglia had replaced the degenerated neurons and resulted in a general shrinking of the whole retina. In this scar-like system of hypertrophic astroglia there were, however, some areas which showed advanced atrophy and necrosis of the glia. All stages of the degeneration of astrocytes were observed in these areas. Some astrocytes showed destruction of their processes (glial fibers) only, while the cell bodies with the eccentric oval nuclei were still visible (Fig. 11*A*). Others were hyalinized (Fig. 11*B*). In this process of degeneration the astrocytes were swollen, the nucleus had disappeared, and all cell structures, including the remnants of the processes, had become hyaline (Fig. 11*B*, *a*). In other necrotic astrocytes all hyalinized remnants of processes had disappeared and a homogeneous round hyaline body was all that remained of each astrocyte (Fig. 11*B*, *c*).

While atrophy of the astroglia was observed in some parts of the peripheral retina, there was a pronounced hypertrophy and proliferation of astroglia in the central retina (including the optic disk). A dense tridimensional network of hypertrophic astroglia with long processes (glial fibers) extended through all retinal layers (Fig. 12) and replaced the degenerated neuronal cells and fibers.

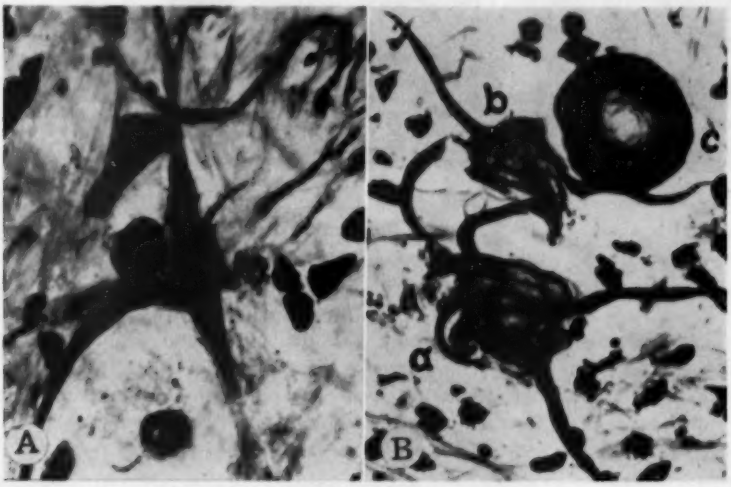


Fig. 11.—*A*, star-shaped partly degenerated body of a retinal astrocyte with eccentric nucleus of the peripheral retina. *B*, more advanced degeneration in retinal astrocytes of the peripheral retina. (*a*) Cell body has become hyalinized and lost its nucleus; some remnants of processes are still visible. (*b*) Further hyalinization. (*c*) Final stage of degeneration of an astrocyte which represents a round hyaline body. Photomicrograph; del Rio Hortega method; × 800.

An impressive finding was the formation of many glial rosettes within the scarified outer layers of the central retina of both eyes (Fig. 9). These rosettes, composed

Fig. 12.—Horizontal section of retina which demonstrates a part of the dense tridimensional network of hypertrophic astroglia with long processes (glial fibers). This network replaced the degenerated neuronal cells and fibers. Photomicrograph; del Rio Hortega method; × 500.

of very undifferentiated cylindrical cells, were arranged horizontally in the retina in close relationship to the hyalinized choriocapillaris (Fig. 7). It must be emphasized that the cells of these rosettes had very long glia-fiber-like processes which could only be demonstrated by Scharenberg's modification of the del Rio Hortega technique.[15] Besides fully developed rosettes with a membrane around the central space, there were incomplete rosettes and band-like formations of the same cylindrical cells. These also occurred as single cells among hypertrophic astroglia, and there were transitional forms between such cells and pathologic astroglia.

Another interesting finding was the bizarre proliferation of perivascular glia of degenerated small retinal blood vessels, which was observed throughout the retina. While the structures of the blood vessels had more or less disappeared, the perivascular glia formed an irregular network of coarse glia fibers around the remnants of the vessels (Fig. 13). Such proliferated glial cells were still present as bizarre fiber structures when the vessel had completely disappeared.

On the inside of the inner limiting membrane of the retina there had developed a new layer of peculiar flat cells with long intertwined processes. This new retinal layer was very dense in the central parts of the retina and around the optic disk (Fig. 14). As more peripheral sections were stained, this layer became thinner and thinner, until it had completely disappeared in the most peripheral regions.

Müller's radial fibers of the retina showed some degenerative changes. Their shape and arrangement were virtually normal in most retinal areas. These fibers showed no proliferation.

4. Changes of the Neurons of the Retina: In the peripheral retina there were practically no neurons left, and a shrunken glial scar which contained pigment and blood vessels had replaced the normal structures.

In the more central retina there were some cones in the areas of the surviving patches of pigment epithelium which were described above. In the areas of destruction of the pigment epithelium, a very dense wall-like formation of hypertrophic astroglia replaced all normal structures of the

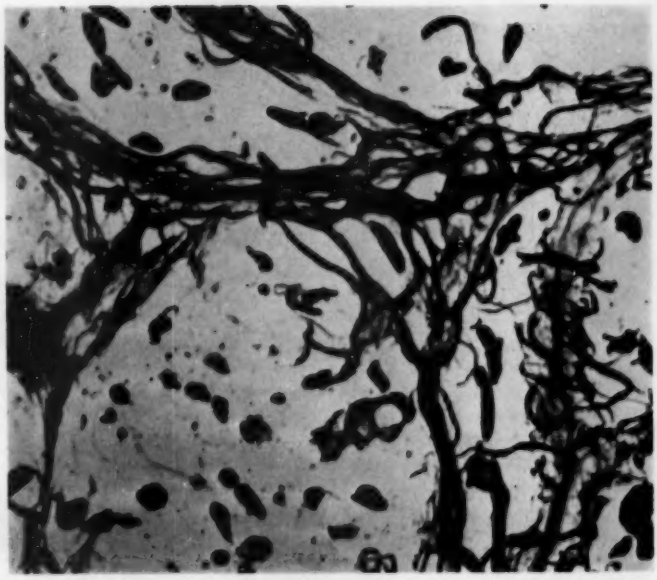


Fig. 13.—Proliferating perivascular glia around remnants of hyalinized blood vessels of the peripheral retina. All black fiber structures represent glial fibers. Photomicrograph; del Rio Hortega method; × 700.

outer retina. No neurons were found in this hypertrophic glia scar of the outer retina. In the inner layers of the central retina, numerous ganglion cells, neurites, and dendrites were observed. But most of the ganglion cells were severely damaged. They were swollen or showed all stages of degeneration and atrophy. Most of the neurites and dendrites were also swollen; some were coiled up, and others were interrupted. Such interrupted nerve fibers of the nerve fiber layer exhibited large terminal swellings (Fig. 15*A*). There were also homogeneous hyaline bodies without contact

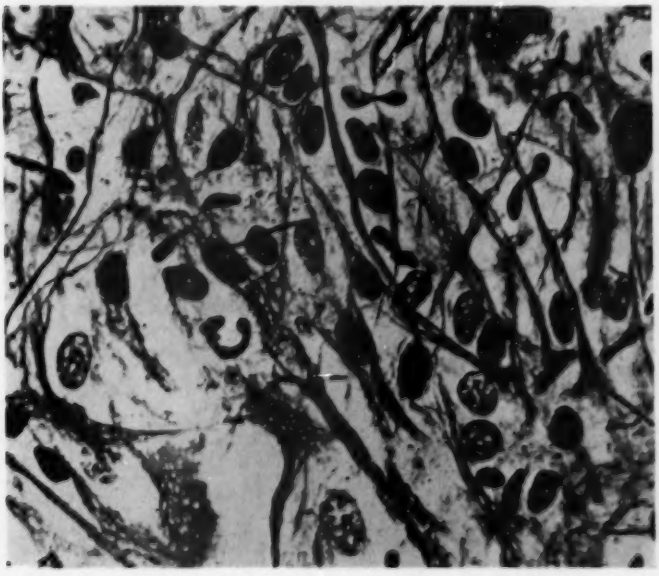


Fig. 14.—New layer of flat hypertrophic astroglia on the inner surface of the internal limiting membrane of the central retina. Horizontal section. Photomicrograph; del Rio Hortega method; × 500.

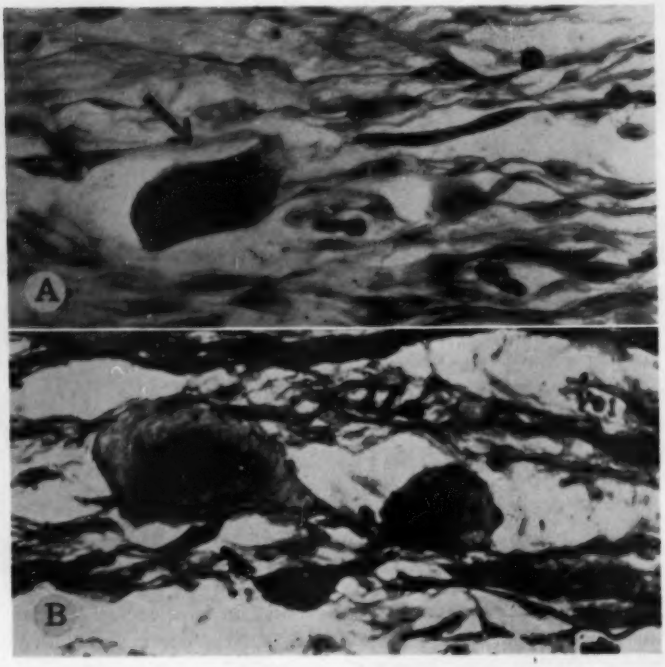


Fig. 15.—*A*, nerve fiber layer of the retina with the terminal swelling of a degenerated and interrupted nerve fiber (arrow). *B*, irregular hyaline bodies of nerve fiber origin in the nerve fiber layer of the retina. Photomicrographs; del Rio Hortega method; × 800.

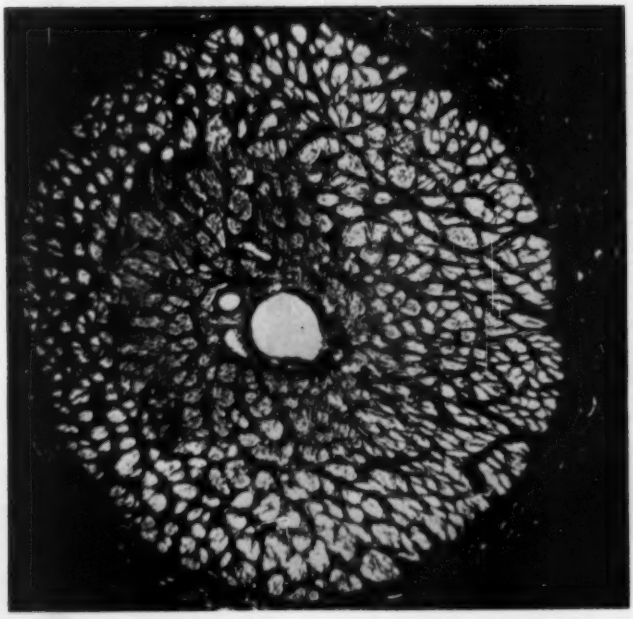


Fig. 16.—Section through optic nerve in the area of the lamina cribrosa. There is increase in connective tissue and glial structures. The artery is very small. Photomicrograph; del Rio Hortega method; × 100.

with nerve fibers in the nerve fiber layer (Fig. 15*B*). Close to the disk, the nerve fiber layer contained very few normal nerve fibers.

5. Changes of the Optic Papilla and Optic Disk: The inner layer of the optic disk was covered by the same dense layer of flat astrocytes with long intertwined processes that was observed on the inside of the internal limiting membrane of the central retina (Fig. 14). There was advanced optic nerve atrophy. The spider cells (special astrocytes of the papilla) showed hypertrophy. The connective tissue structures of the lamina cribrosa were increased (Fig. 16), and their foramina, which normally contain the nerve fibers, were filled by scarified astroglia. The lumen of the central artery was much smaller than normal.

The optic nerve contained only a few nerve fibers. The astroglia, however, were hypertrophic, and the network of the glial fibers filled the space of the broken-down neurites (Fig. 17 *A* and *B*). Surprisingly, there was no hypertrophy or phagocytic activity of the microglia. The latter cells, which represent the phagocytes of the optic nerve, were normal and not increased in number (Fig. 18).

Comment

The essential pathology of the presented case was composed of very advanced changes in the retina, in the choroid, and in the optic nerve of both eyes. There also were advanced cataracts. In the retina there was an almost complete loss of the pigment epithelium and of the visual cells. Extensive degeneration of the neurons, gliosis,

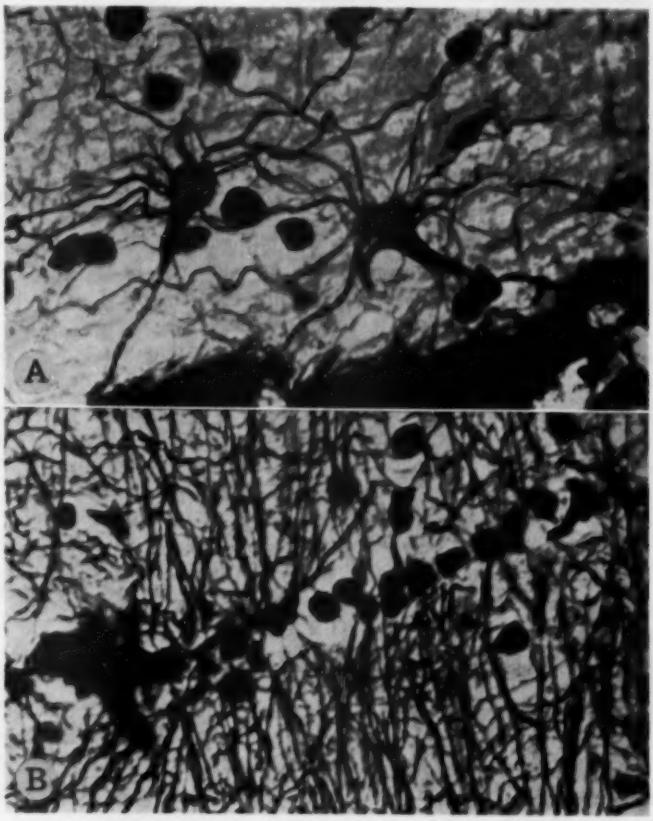


Fig. 17.—*A*, two hypertrophic astrocytes of the optic nerve. The processes of these cells (glial fibers) are clearly visible, and two of them may be seen in contact with the connective tissue structures of blood vessels (lower right corner of picture). *B*, system of hypertrophic astroglia of the optic nerve. The glial fibers are clearly visible, while the nerve fibers are only faintly stained. Photomicrographs; del Rio Hortega method; ×600(*A*) and ×250(*B*).

pigment invasion, and vascular occlusion and atrophy extended throughout the retina. In the choroid, hyaline degeneration of the choriocapillaris was an outstanding histologic finding. The optic nerve showed atrophy and gliosis.

Many round pigment-filled cells were observed all through the retina. It was not possible to decide whether these cells represented pigment-filled retinal phagocytes (microglia) or migrating elements of the pigment epithelium.

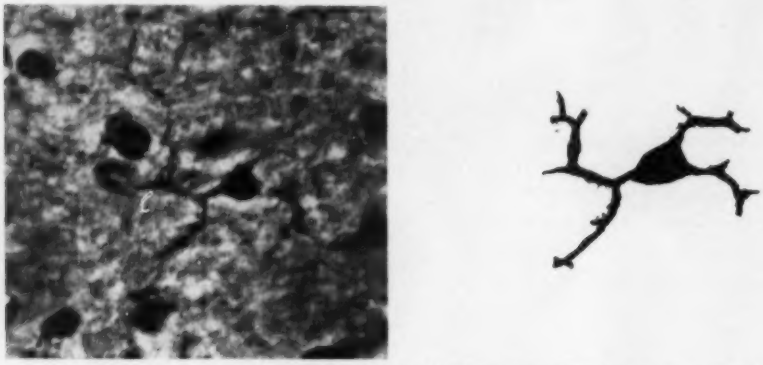


Fig. 18.—*A*, photomicrograph and, *B*, drawing reconstruction of a microglia cell of the optic nerve as seen in this case. This cell appears to be normal. Photomicrograph; del Rio Hortega method; ×800.

The complete degeneration of the peripheral pigment epithelium, the migration of pigment into the retina, and its accumulation around the blood vessels has often been reported in advanced cases of retinitis pigmentosa. The pigment sheathing of the degenerated blood vessels is generally regarded as the cause of the so-called bone-corpuscle-like formations which are observed ophthalmoscopically. In the central retina of this case, visual cells survived only in areas of normally arranged pigment epithelium. This finding again indicates the close relationship in function and pathology of the pigment epithelium and the visual cells. In all areas of destruction of the pigment epithelium a reactive wall-like zone of hypertrophic retinal astroglia had replaced the neuronal cells. This glial reaction is nonspecific and can be observed in eye pathology when the pigment epithelium disappears and retinal (neuroectodermal) tissue comes in direct contact with the mesodermal tissue of the choroid (Wolter [20]).

The blood vessels of the retina and choroid of this case showed very advanced degeneration. Apparently, the degenerative process began with deposition of hyaline in the vessel walls and involved the small vessels of the retina and choroid most severely. In the later stages many of these vessels represented solid strands of hyaline connective tissue. At the final stage there was complete disappearance of the blood vessels, and their site could only be assumed by virtue of the remaining cuffs of perivascularly deposited pigment and proliferating perivascular glia.

The obliterative hyaline degeneration of the retinal vessels in advanced cases has been reported frequently by others. However, considerable differences in findings of the state of the choriocapillaris have been noted. Some authors reported a more or less complete disappearance of the choriocapillaris (Landolt,[1] Wagenmann,[2] Deutschmann,[28] Koyanagi,[29] Lister,[3] Gonin,[7] Ascher,[10] Lucas [30]). But in the majority of cases, the choriocapillaris was normal—

even in extremely advanced cases of this disease (Stock,[4] Verhoeff,[9] Suganumba,[8] Cogan,[11] Lucas [30]). A complete hyalinization of the whole network of the choriocapillaris, as in the present case, has not been previously described.

Earlier investigators suggested that the retinal degeneration in retinitis pigmentosa may be secondary to a progressive degeneration of the vessels of the choriocapillaris (Landolt,[1] Deutschmann,[28] Gonin,[7] Nettleship,[31] Hepburn [32]). Wagenmann [33] even demonstrated that experimental interruption of the ciliary arteries in animals resulted in a retinitis-pigmentosa-like ophthalmoscopic picture. Other authors, however, have shown that the choriocapillaris may remain normal even in the very advanced stages of retinitis pigmentosa. They, therefore, considered the disease to be a primary hereditary abiotrophic defect or the result of an endocrine dysfunction in the neuroepithelium (see Adler and McDonald [34]). Ascher [10] has suggested that there may exist two separate forms of retinitis pigmentosa, one mesodermal (chorioidal) and the other neuroectodermal (retinal) (see Duke-Elder,[12] p. 2777). I believe that the present case could be of this first mesodermal type. However, it cannot be considered to be evidence for the existence of this type, since all changes are much too advanced. As Cogan [11] has emphasized, it is not possible in advanced stages of retinitis pigmentosa to differentiate the primary lesion—if this can be found in a histologic slide at all—from the secondary complications.

The pathology of the astroglia of the retina is a new field of ophthalmological investigation. The normal pattern and some of the common pathological changes have been histologically demonstrated only recently (Wolter,[17,20,22,25] Liss [27]). The present case exhibited many different stages of reactions of the astroglia. In various areas, there were hypertrophy, proliferation, scar-formation, hyaline degeneration, and atrophy. It is interesting to note that degeneration of astrocytes may result in the formation of hyaline bodies which are similar to those of nerve fiber origin (Wolter [21]).

The finding of typical rosettes in the glial scar of the outer layers of the central retina somewhat disturbs the current understanding of the nature and significance of retinal rosettes in general. In the present case there were transitional forms between the hypertrophic astroglia and the cylindric cells of the rosettes and the rosettes possessed long glia-fiber-like processes. These facts are contrary to the theory that rosettes always develop from the neuroepithelium and suggest the possibility that the rosettes in this case represent reactive formations of pathological astroglia (see Wolter,[20,35] Seefelder,[36] Teng and Katzin,[37] Meyer-Schwickerath [38]).

The nature of the special perivascular glia of the human retina is not yet understood.[17,20] These cells may belong to the group of special astroglia of the human retina. However, they are also somewhat similar to the oligodendrocytes found in other parts of the nervous system. The bizarre proliferation of surviving cells of this kind around atrophic blood vessels of the retina in this case is an important histologic detail, although its explanation is far from clear.

Friedenwald [13] first described "peculiar flat endothelium-like cells" at the inner surface of the internal limiting membrane of the human retina which proliferate in degenerative and inflammatory conditions of the eye. Later, it was demonstrated that these flat cells are special astrocytes which normally represent only a very loose cellular network. These cells proliferate under certain pathological conditions and then form a new layer on the inner surface of the retina (Wolter [39]). The existence of such a new-formed glial membrane was very impressive in the central retina of the present case. It may be mentioned here that in Figures 1 and 12 of Cogan's paper [11] there are very similar membranes on the inner retinal surface in retinitis pigmentosa.

Verhoeff [9] described an extensive proliferation of the radial fibers of Müller in his case. Such a proliferation was not seen in the present case. Müller's elements showed some degeneration but were generally in their normal position and arrangement. The active hypertrophic elements of all areas of dense glial scar formation in this case were retinal astrocytes.

The neuronal damage in the present case was very extensive. The layer of the visual cells had disappeared almost completely. Only centrally, there still were some cones. The inner retinal layers were much better preserved than the outer layers. Special nerve staining methods also revealed, however, all stages of degeneration in ganglion cells and nerve fibers. There were virtually no normal nervous structures left all through the retina.

The present case exhibited advanced optic nerve atrophy. Stock [4] published a picture of a section through the optic nerve of one of his cases which shows the same pathology as the present case: degeneration of most of the nerve fibers and hypertrophy of the glial and connective tissue structures. It is reasonable to assume in the present case that the typical phenomenon of the "waxy pallor" of the optic disk is the effect of a combination of the new-formed layer of astrocytes on the inner surface of the papilla, of the nerve fiber degeneration, and of the scar-formation of glia and connective tissue within the optic nerve head. Surprisingly, the microglia of the optic nerve histologically showed neither phagocytic activity nor increase in number. The advanced stage of the optic nerve atrophy and the chronicity of the whole process may explain this finding.

Summary

A histological study of both eyes of an advanced case of retinitis pigmentosa is presented. The silver carbonate methods of del Rio Hortega were used to demonstrate new details of the pathology of the retina, choroid, and optic nerve.

University Hospital.

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The Protein Components of Human Tears

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Introduction

Recently McEwen and Kimura have employed filter paper electrophoresis to separate the proteins present in tears.[1] Their analysis showed the presence of at least three components in "normal" tears. One of these components was positively charged at pH 7.8 and was identified as lysozyme. Smolens, Leopold, and Parker,[2] studying tears induced by a lacrimating agent, benzyl bromide, report the presence of four electrophoretic fractions, three of which were basic at pH 7.9. Caselli and Schumacher report the presence of five electrophoretic fractions, only one of which was positively charged at pH 8.6.[3]

In order to clarify this discrepancy, and in particular to study the effect of irritants, tears produced as a response to a variety of stimuli were studied.

Experimental Method

The tears were obtained from the conjunctival sac by the use of ultramicropipets of the Kirk type * (Fig. 1). In certain cases, notably with children and during profuse lacrimation, it was not possible to obtain the tears from the sac, in which case the tears were obtained with the pipets as they spilled over the eyelids.

The tears studied include those induced by emotional stress both in children and adults, by idiopathic excessive tearing, and by irritation caused by α-chloroacetophenone, onion vapors, or air pollutants.

The tears were studied electrophoretically. Filter paper electrophoresis was carried out on individual samples in a buffer at pH 8.5, containing 0.05 M barbital, 0.025 M NaCl, and 0.025 M Na acetate. The tears were analyzed in the Spinco Model R electrophoresis unit the same day they were obtained. Approximately 2 ma. were passed through each strip for 16 hours at room temperature. The strips were then quickly dried in a Chromatocab oven at 100 C. The proteins were stained with bromophenol blue followed by acid washes in the usual manner.[4] Semiquantitative values were obtained for the per cent distribution of protein in tears as follows: The paper strips were cut into 0.5 cm. sections. The dye bound in each section was eluted with 3 cc. of 0.1 N NaOH at room temperature for two hours. The optical density of the resulting solution was determined at 545 mμ in a Coleman Junior spectrophotometer. By assuming that the optical density was proportional to the amount of protein on a paper section the per cent distribution of protein in the various fractions could be obtained.

Larger pooled samples of emotion- and irritation-induced tears, as well as those resulting from idiopathic lacrimation, were obtained. These samples were stored at 4 C in the presence of thymol until sufficient quantities were available to permit use of the 2 ml. Tiselius cell. The Spinco Model

Figure 1

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* Kensington Scientific Corp., 98 Rincon Rd., Berkeley 7, Calif.

H electrophoresis apparatus was employed, using barbital-NaCl buffer, pH 8.5, ionic strength 0.1.

Results

Paper electrophoresis of tears disclosed the presence of components with the mobility of serum albumin, serum globulin, and lysozyme. In general, the globulins resolved into two or three bands.

Figure 2 shows typical patterns obtained for emotional tears and tears induced by onion vapors. Smooth curves have been drawn through the points obtained by plotting optical density against distance. While the patterns for the two types of tears are similar, there is a diminution in the content of albumin in the irritant-induced tears.

Analysis of the patterns obtained disclosed that it was impossible, using this tool, to distinguish tears obtained by emotions and tears produced in excessive amounts without obvious cause. Likewise, the tears induced by the various irritants were indistinguishable. Consequently, the samples were considered in one of two groups: irritant-induced tears or idiopathic-emotional tears. It is believed that this latter group more closely approximates the fluid normally covering the surface of the cornea. Consequently, this group also will be referred to as the "normal" tears.

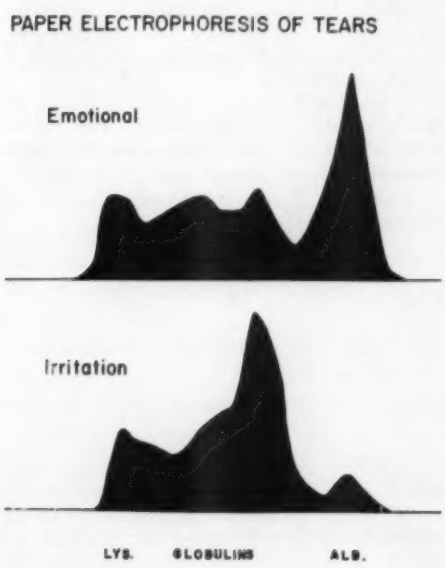

Figure 2

The percentage distribution of protein in the three main groups—albumin, globulin and lysozyme—was determined, and the results are shown in the Table. No attempt was made to subdivide the globulins. The primary effect is the decrease in albumin in the irritation-induced tears, which is reflected as a decrease in albumin and increase in the other fractions when they are expressed on a per cent basis.

Protein Composition of Tears

	% Albumin	% Globulin	% Lysozyme
"Normal" tears (21)*	38.8	44.8	16.4
Irritant-induced tears (12)	19.3	54.0	26.7

*Number of subjects is given in parentheses.

The results obtained with the Spinco Model H electrophoresis apparatus (Fig. 3) show the presence of an albumin, three globulin components, and lysozyme, with again a dimunition of albumin in the irritant-induced tears. An unexpected peak, however, was seen. It moved very slowly to the cathode at pH 8.6. Since this component was equally prominent in both the ascending and descending limb, it has tentatively been designated as a second basic protein. The inability to obtain large quantities of tears precludes determination, at this time, of the contribution of the salt anomolies to this component. The fact that only one basic protein is seen on paper under comparable conditions of pH and ionic strength may be attributed to the difficulties in obtaining satisfactory movement of many basic proteins owing to the charge on the paper.

Comment

Emotional tears were obtained from patients ranging in age from 6 months to 50 years. No systematic differences with age were seen. It was noted that the amount of tears secreted during emotional disturb-

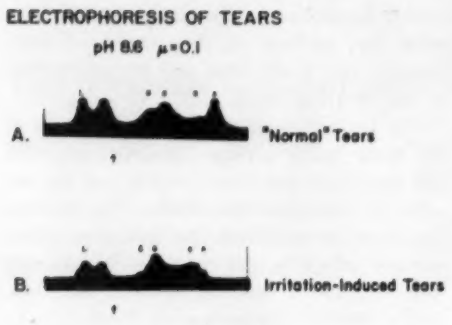

Figure 3

ances frequently was much greater than that obtained by irritants in this study. The flow of irritant-induced tears usually began profusely and then stopped abruptly as the threshold for stimulation rose. Although the amount of emotional tears exceeded that secreted in response to irritation, in this study, the amount of protein in the former was higher, being about 0.6% while the latter values were approximately 0.4%. Direct extirpation of human lacrimal tissue followed by extraction with isotonic saline failed to demonstrate the presence of appreciable stored lysozyme. Preliminary experiments in which lacrimal tissue was incubated under conditions favorable to protein synthesis also failed to demonstrate lysozyme formation. This may mean that it is formed in vivo by the lacrimal gland as tears are secreted or that another gland is responsible for its production.

While the fluid studied obviously is the resultant secretion of several glands, this study demonstrates a type of double innervation of "tear" secretion in which each pathway results in a different secretion. This work suggests that further information may be gained by studying the differential production of albumin and lysozyme (or globulins) under a variety of experimental conditions, including the influence of sympathetic and parasympathetic nervous stimulation.

Summary

The proteins of tears produced as the result of diverse stimuli have been studied electrophoretically.

The presence of albumin, lysozyme, and three globulins has been detected.

Irritant-induced tears contain appreciably less albumin than emotional tears or those produced by idiopathic excessive lacrimation.

It is suggested that additional information regarding tear formation may be gained by studying the differential production of lysozyme and albumin.

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University of California Medical Center (24).

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Effect of Temporary Occlusion of the Aorta on the Electroretinogram

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During clinical electroretinographic examination of patients we observed a new phenomenon which we called "exhaustion phenomenon" (*phénomène d'épuisement*). This phenomenon has been further studied in cats.

Briefly, it is as follows: If the dark-adapted cat retina is stimulated intermittently with light of 50 lux intensity (measured at the cornea), one-tenth second duration, and one second frequency, the b-potential in the ERG is practically the same for each stimulus. If, however, the procedure is repeated on a cat with impaired oxygen supply, the b-potentials on intermittent stimulation become progressively smaller and finally may almost disappear. If the intermittent stimulation is now suspended for a time, e. g., one minute, while the cat still remains in darkness, the b-potential will be found to have returned to its former level, but on intermittent stimulation it will again become smaller. We ascribed this phenomenon to a delayed recovery of the adaption state in hypoxemia. The fact that dark adaptation is disturbed in anoxemia has been convincingly demonstrated by numerous investigators.[1,2] In our experiments we cut down the animal's oxygen supply by applying artificial but insufficient respiration.

In connection with this investigation we became interested in methods for the reduction or interruption of oxygen supply to the retina. Ten Cate and Horsten [2-6] have done much work in this field with temporary occlusion of the aorta and observation of the effects on the electroencephalogram. The objects of their investigation have been to answer the following questions: (1) How long after clamping of the aorta does the EEG disappear? (2) How long can the occlusion be continued for the EEG still to reappear after removal of the clamp? Ten Cate and Horsten [2] also showed that in the cat it is not sufficient to occlude the carotids only, as the brain then still receives blood from the vertebral arteries and the anterior spinal artery.

We have shown that the same applies to the ERG. The classical component analysis of Granit,[13] in which the b-wave is selectively caused to disappear by occlusion of both carotids, succeeds only in decerebrated cats with low blood pressure. We have observed that in nondecerebrate cats the effect of carotid occlusion is comparatively slight and certainly insufficient to cause disappearance of the b-potential.

In view of the parallels so frequently drawn between retina and cerebrum, we considered it worth while to study the effects of temporary occlusion of the aorta on the ERG and to compare these with the effects on the EEG. The questions we set out to answer were thus the following: (1) How long after clamping of the aorta does the ERG disappear? (2) How long can the occlusion be continued for the ERG still to reappear after removal of the clamp?

Method

The experiments were carried out on 10 cats. Our reason for choosing the cat was that its retina, as pointed out by Granit,

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strongly resembles the periphery of the human retina, while the aims of our investigation included the collection of data for clinical electroretinography.

The animals were anesthetized with pentobarbital sodium intraperitoneally. Needles were inserted occipitally through the skull for recording of the EEG. The ECG was also recorded. Lid holders were introduced, and the third eyelid was drawn to one side with a suture. For recording of the ERG the indifferent electrode was inserted into the skin of the forehead. An active electrode for the ERG recording was inserted into the cornea of each eye in an "intralamellary," i. e., nonperforating, manner, at the temporal side about 2 mm. from the limbus corneae. This last point is connected with Karpe's [14] remarks on the registration of the ERG with local leads; he states that this method is liable to give artefacts but that these can be avoided if the electrodes are not inserted into the limbus corneae itself but into the corneal tissue at a few millimeters distance from it. Further, in our animals the pupils were dilated beforehand with atropine, in order to avoid the artefacts which are ascribed by Karpe to contraction of the pupil.

Before the experiment the cat was kept for about 20 minutes in the dark. The operation was also carried out in darkness, with only local illumination of the operative field. In this way the cat had been dark-adapted for at least 30 minutes before the actual recordings were started. The ERG was then registered after application of a luminous stimulus of 50 lux, measured at the cornea, with a duration of one-tenth second. This stimulus was supplied by a partially modified Terry lamp fitted with an automatically operated Ibsor shutter. The frequency of stimulation—every 3 seconds—was regulated by metronome beats. The flash was registered by a photoelectric cell. Amplification and recording were effected by a Schwarzer electroencephalograph for 12-channel recording; the ERG of each eye, the EEG, the ECG, and the light flashes via the photocell (on 2 channels) were registered simultaneously, while the time in seconds was also marked. After this the aorta was exposed by the method described by Ten Cate and Horsten and clamped as close as possible to the heart. This procedure necessitates artificial respiration. The heart continues to beat, because—as shown by Horsten and Wöstman,[7] with injections of radioactive phosphorus—the coronary circulation is maintained at a normal or slightly increased level. The operation was carried out in a dark room, the only source of light being a "hammerlamp" (Zeiss), such as is used in ophthalmological operations, while the cat's head was screened in such a manner as to ensure that the dark adaption was not disturbed.

Under these conditions it is possible to keep the aorta clamped for 10 minutes, or even longer, without ill-effects; our shortest time was 7½ minutes, and the longest, 13½ minutes. In 2 of the 10 experiments a Tscherning filter No. 1½ was placed in front of one eye, reducing the intensity of illumination of this eye to 1/34 of that of the other, i. e., approximately 1½ lux.

As soon as the experiment had proceeded to the point at which the aorta could be clamped, the registration apparatus was set in action and the eyes were stimulated with a flash every three seconds. The aorta was then clamped, and after 7½ to 13½ minutes the clamp was removed. The graphic recording obtained in this way describes the course of the entire experiment.

Results

A complete survey of the results in experiments on 10 cats is given in Table 1. In this we see that in four experiments it was not possible to register the return of the ERG because the animal died during the experiment.

For the sake of clarity we shall consider the results under two headings: (1) disappearance of the ERG after occlusion of the aorta and (2) its return after removal of the clamp.

TABLE 1.—*Effects of Temporary Occlusion of the Aorta on EEG and ERG*

Cat	Stimulus Intensity (Time 0.1 Sec.), Lux	EEG Disappeared After	B-Pot. 50% After	B-Pot. Disappeared After	Neg. Pot. Disappeared	Duration of Occlusion	EEG Recovered	1st Sign of Neg. Pot.	1st Sign of B-Pot.	B-Pot. 50%	B-Pot. 100%	Remarks
1	50		17″	49″	(4′-7′)	10′		6″	60″	1′52″	3′2″	EEG not registered
	30		18″	48″	(4′-7′)			6″	60″	1′50″	4′2″	
2	50	12″	15″	42″	4′39″							Cardiac fibrillation
	50		7″	46″	4′39″							4½ min. after occlusion
3	50		17″	50″	5′			12″	88″	2′17″	2′41″	Pump temporarily out of action?
	30	23″	11″	38″	2′46″	10′	–	15″	2′14″	2′29″	2′45″	
4	50	23″	12″	40″	3′30″	6′?	–	1′18″				Heart action poor; cat died during recovery period
	50		15″	51″	?			1′27″				
5	50	24″	14″	61″	2′36″	10′	–	7″				Cardiac fibrillation after removal of clamp
	50		19″	61″	2′36″			4′				
6	50	20″	25″	51″	7′15″	8′	–	3″	45″	73″	3′12″	
	30		23″	53″	6′5″			3″	45″	70″	3′12″	
7	25	20″	29″	60″	8′34″							Cat died during occlusion
	25		27″	57″	8′34″							
8	1.5	26″	27″	3′		13′30″	–	–	2′20″	4′30″		
	50		27″	61″	7′			11″	2′29″	8′2″		
9	30	55″	16″	59″	3′15″	7′30″	+	3″	71″	1′39″		
	50		16″	59″	3′15″			3″	77″		3′6″	
10	1.5	2′36″		4′		10′			47″	2′31″		Pump not working properly; EEG maintained too long
	50		25″	2′61″	8′			3″	50″	1′43″	4′12″	

TABLE 2.—*Disappearance of Electrical Potentials After Occlusion of the Aorta*

EEG	ERG		
	B-Pot. 50%	B-Pot. Disappeared	Neg. Pot. Disappeared
Stimulus intensity 50 lux; duration 0.1 sec. 20-26"	11-27"	38-61"	2'46"-7'15"
Stimulus intensity 1 ½ lux; duration 0.1 sec. 26"	27"	3' (?)	--

For judgment of the disappearance of the ERG we took the disappearance of the EEG as a standard of comparison. Ten Cate and Horsten found that the EEG disappeared after an average of 20 seconds from the clamping of the aorta. For judgment of the disappearance of the ERG we therefore used only those curves in which the disappearance of the EEG fell approximately in the time range between 20 and 26 seconds after clamping. The results are given in Table 2. This shows that the positive b-wave and the negative potential of the ERG behave differently. With a light stimulus of 50 lux the b-wave has completely disappeared after 38 to 61 seconds; with the weak stimulus of 1½ lux there is still a positive potential demonstrable up to 3 minutes after application of the clamp. The form of the latter wave, is however, somewhat different from that of the usual b-wave; it is broadened and flattened (see Fig. 2). The negative potential appears only with the stimulus of 50 lux and is absent with the weak stimulus. It is much more resistant than the positive potential and does not disappear until after a period ranging from 2 minutes 46 seconds to 7 minutes 15 seconds.

An investigation that is in some respects comparable with ours is that of Noell and Chinn.[9] These workers produced anoxia in rabbits by causing them to inhale pure nitrogen. With respect to the ERG in these animals they state that 15 to 25 minutes of anoxia were necessary to give a completely negative ERG. With one or two stimuli per hour this negative component was still demonstrable after several hours. The description of these experiments, however, is not very clear. In the cat we found much shorter times for the disappearance of the positive and negative components of the ERG. Among the curves relating to experiments on various mammals, as published later by Noell,[10] we found one relating to the cat. Here the asphyxia was induced by artificial raising of the intraocular pressure

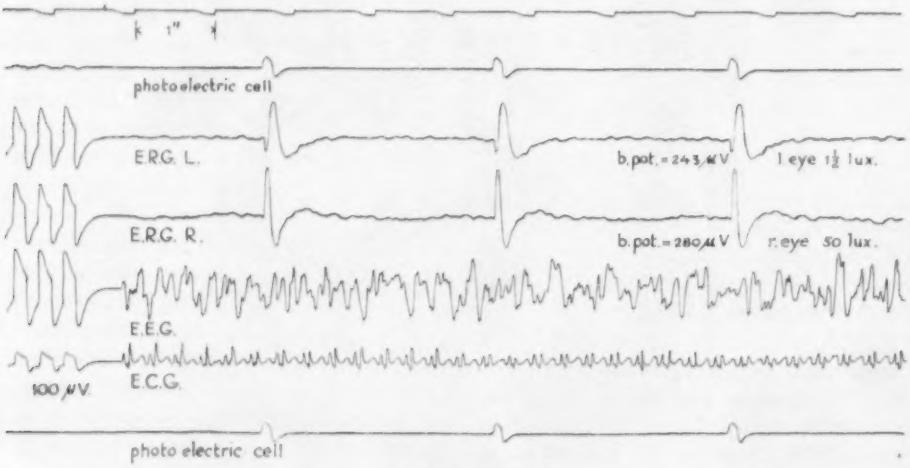

Figure 1

to a high level. If we are correct in our interpretation of this curve, Noell found the positive component of the ERG of the cat to have practically disappeared after 50 seconds of asphyxia. The time elapsing before the negative component disappeared is not given. It is, however, stated that for the cat the time elapsing before the a-wave was reduced to 30% of its original value was more than 200 seconds.

Figures 1 and 2 show some portions of the tracing for Cat 8 (Table 1). Figure 1 gives the ERG's for the right and left eyes before the aorta was clamped. A neutral gray Tscherning filter was placed before the left eye, so that the light intensity on this eye was 1½ lux, while the right eye received 50 lux. Rather surprisingly, the eye that received the weak stimulus shows a "negative a-wave" and, further, in this eye the highest point of the b-wave comes later than in the eye receiving 50 lux. Upon occlusion of the aorta this "a-wave" disappears simultaneously with the diminution of the b-wave. It thus behaves differently from the resistant negative potential that appears with the strong stimulus and is characterized by its long persistence. When the b-potential has decreased to 50% of the initial value, this "a-wave" with the weak stimulus has practically disappeared (Fig. 3).

The events after removal of the clamp from the aorta are summarized in Table 3. Only in one case did we see the EEG return; this was after clamping for seven and one-half minutes. From this Table we see further that the negative potential not only takes longer to disappear than the positive potential but also returns much more quickly. With the stimulus of 50 lux the negative potential often returned after as little as 3 seconds; after the occlusion for 13½ minutes (Cat 8) this time was 11 seconds (Fig. 4). The first sign of a returning b-potential appeared much later and after a time that depended on the duration of occlusion and ranged from about one to two and one-half minutes after removal of the clamp.

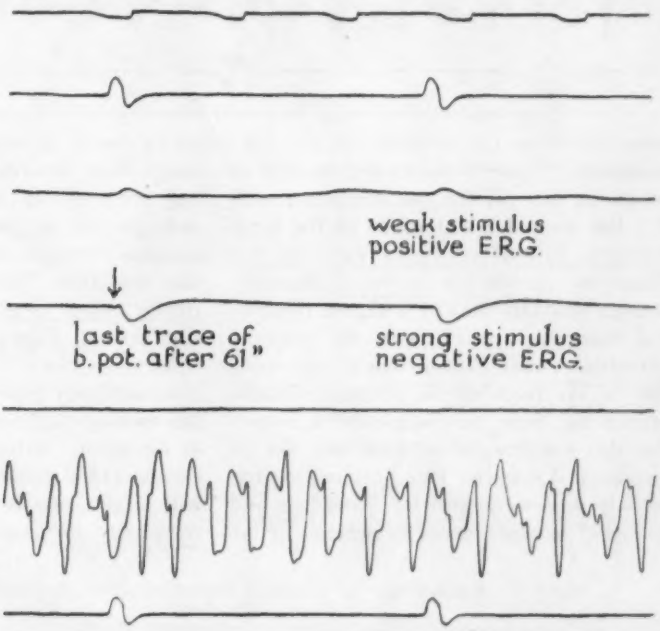

Figure 2

Figure 5 shows the moment at which the first sign of the returning b-potential be-

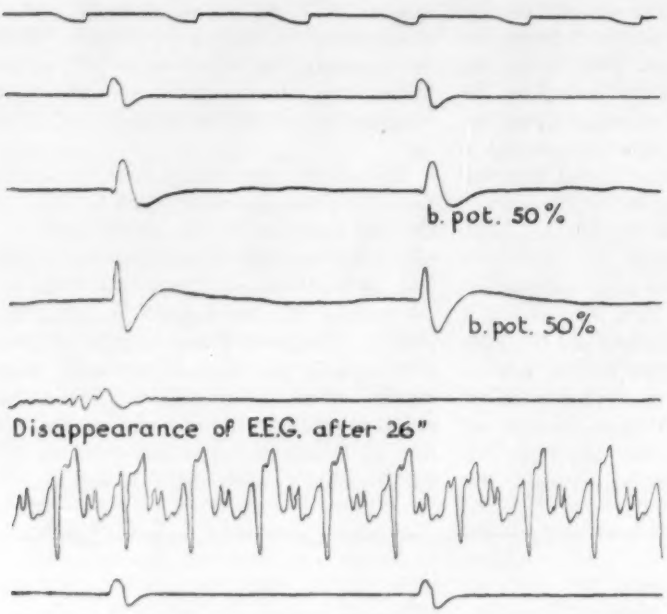

Figure 3

came visible in Cat 8 (occlusion for 13½ minutes). Figure 6 shows the moment at which in this cat the eye stimulated with 1½ lux showed a restoration of the b-potential to 50% of its original value. In this Figure we see that the eye that received the weaker stimulus showed a higher b-potential than the eye receiving the stronger stimulus. Closer examination of the curve for the eye receiving the stronger stimulus reveals not only an a-wave and a b-wave but also something that looks very like an exaggerated c-wave. This phenomenon has already been mentioned by Bornschein and Zwiauer [1] in experiments on ischemia of the retina due to increase of intraocular pressure. They describe the observation, during recovery of the retina from such ischemia, of an excessive "c-wave" at a stimulus duration with which this normally does not occur. This phenomenon was very clearly visible in all our curves; it can be seen even in Figure 5.

In those cases in which the b-potential was completely restored to its original value, this took up to three minutes after removal of the clamp. After the long period of occlusion (13½ minutes), however, the original height of the b-potential was not completely restored. There was also an-

TABLE 3.—*Reappearance of Electrical Potentials After Removal of Clamp from the Aorta*

Duration of Occlusion	EEG	ERG			
		Neg. Pot.	B-Pot.	B-Pot. 50%	B-Pot. 100%
Stimulus intensity 50 lux; duration 0.1 sec.					
7'30"	+	3"	71-77"	1'30"	3'6"
8'	–	3"	48"	73-79"	3'12"
10'	–	3-15"	59"-2'14"	1'43"-2'29"	2'41"-4'12"
13'30"	–	11"	2'26"	8'2"	..
Stimulus intensity 1½ lux; duration 0.1 sec.					
13'30"	–	..	2'20"	4'36"	..

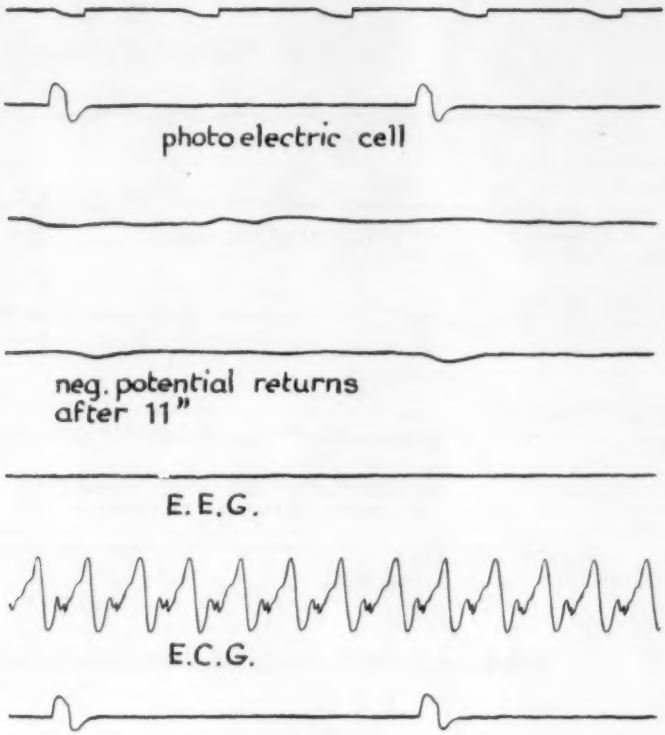

Figure 4

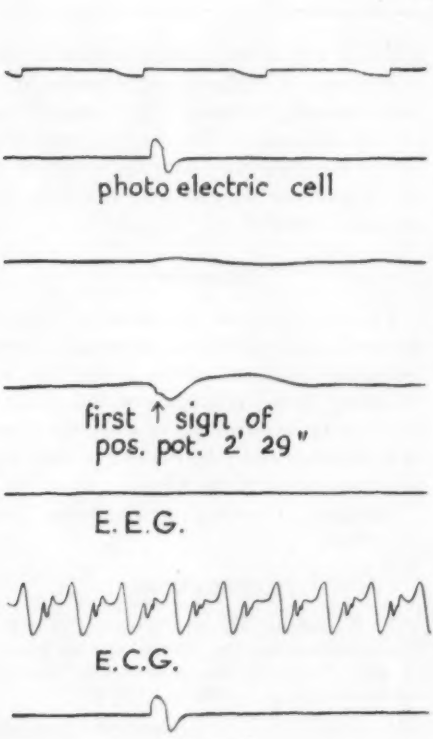

Figure 5

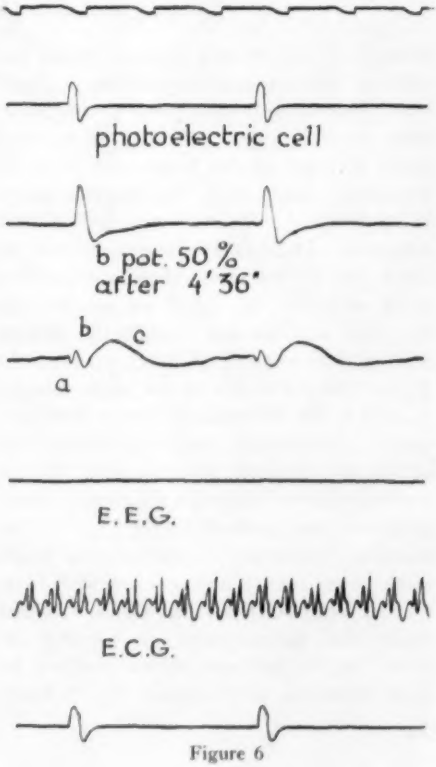

Figure 6

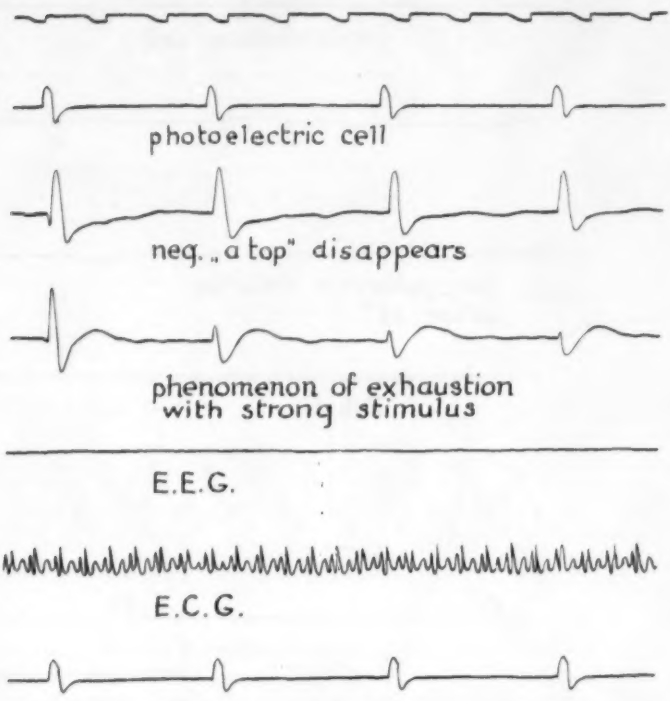

Figure 7

other fact that showed that the retina had suffered damage, and that was the "exhaustion" phenomenon mentioned at the beginning of this paper. This consists in a rapid decrease of the b-potential after intermittent illumination, the original height being restored only after a period of dark adaption. The phenomenon is absent or much less evident after stimulation with a weak stimulus. In Cat 8 we see this exhaustion phenomenon excellently demonstrated after removal of the clamp from the aorta. The eye receiving the weak stimulus reacted to the intermittent (every three seconds) illumination with b-potentials of practically constant size, whereas the eye receiving 50 lux showed a progressive diminution of the b-potential (see Fig. 7), followed by restoration to the original height after about one minute of renewed adaption in total darkness. In Figure 7, which shows this phenomenon, we see that the curve for the left eye, which received the weak stimulus, again shows the "a-wave" observed before the commencement of the experiment. With the second stimulus, after three seconds, however, this "a-wave" has already disappeared. Its disappearance thus occurs simultaneously with the reduction of the b-potential of the eye receiving the stronger stimulus.

Summary

The resistance of the retina to oxygen deficiency was studied in experiments with temporary occlusion of the aorta. The relationship to the resistance of the cerebral cortex was investigated, as were the times of appearance and reappearance of the various components of the ERG.

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The Electroretinogram in Detachment of the Retina

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In an earlier paper (Karpe and Rendahl, 1952), an account was given of 100 cases of detachment of the retina, in which the course of the disease was studied with the electroretinogram (ERG). Since then, an additional 150 cases have been followed with the ERG at the same eye clinic. It has therefore been considered expedient to analyze these total 250 cases in order to complement the earlier investigation, to confirm its results, and to attempt further elucidation of a number of essential problems regarding the nature of retinal detachment.

In the aforementioned paper, it was first of all shown that, as could be expected, retinal detachment is associated with a marked deterioration in the ERG and that this deterioration runs to some extent parallel to the size of the detached area. The investigation nevertheless showed that some additional factor must exist which determines the size of the b-potential on the ERG in these cases, a factor which was denoted as the general condition, or "vitality," of the retina. On the basis of these observations, the authors considered that they could ascribe some prognostic value to the ERG, particularly in cases that were hard to evaluate and in which doubts were felt regarding the form of treatment to be advised. Finally, it was found that a tendency was present in these patients to a subnormal ERG in the other, clinically healthy, eye as well. This was interpreted as a suspected predisposition to retinal detachment in these patients.

In a recent publication, François and de Rouck (1955) reported their experience in 26 cases of retinal detachment combined with myopia. In the first section of the paper, the authors presented a normal series of myopic persons, and they were able to show that the ERG is normal in uncomplicated myopia. In malignant myopia (60 cases) they found in 75% of the cases a subnormal ERG, i. e., a b-potential less than 0.25 mv. according to François' delimitation of the normal group of ERG's.

A fact of great interest is the authors' observation that, in cases of malignant myopia, a subnormal ERG is found at an early stage. This subsequently remains unaltered for a long time, despite progression of the myopia. Further deterioration of the ERG is found only in advanced cases, with severe atrophic changes in the retina.

The authors interpreted their results as an indication that both the retinal condition (manifested partly as a subnormal ERG) and the error of refraction are dependent on a common "biologic factor." They also stated the investigation to be a strong argument against a more mechanical interpretation, according to which the eyeball becomes successively elongated, and the retina therewith increasingly stretched, since in this case a successive deterioration in the ERG should be noted.

The authors then gave an account of 26 cases of retinal detachment in myopic eyes. In 14 cases only the results before an eventual operation were given. In these cases, it was stated that the ERG did not deteriorate to the same degree in traumatic detachment as in idiopathic detachment.

In 12 cases the ERG was recorded postoperatively (in 2 cases the preoperative ERG was also given). Operation was successful in every case. In some cases the ERG was extinguished despite the fact that

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operation had resulted in reattachment and satisfactory function.

In two cases the authors reported an improvement in the ERG postoperatively. In one of them the ERG had, it is true, been recorded before the actual operation (sclerectomy) but not until after three diathermy cauterizations. In the other, the ERG was extinguished before operation; postoperatively, the b-potential was 0.25 mv. The b-potential of the other, healthy, eye was 0.41 mv. at the first examination and 0.26 mv. at the second. Since no explanation was given of this variation in the ERG of the unaffected eye, there is perhaps reason to suspect some recording error in this case.

Summarizing their results, François and de Rouck stated that—as pointed out by Karpe and Rendahl—the ERG deteriorates in retinal detachment, both in relation to the size of the detached area and as a result of a decline in the "vitality" of the retina (which, in cases of myopia, can be explained by the error of refraction). They also regarded it as established that, in many cases, there is a considerable improvement in the ERG after a successful operation. Since reattachment was observed even in cases with an extinguished ERG, the examination was regarded to lack any prognostic value.

In examination of the other, clinically healthy but myopic, eye, François and de Rouck found no other deterioration in the ERG than that due to the myopia. Consequently, the authors expressed their doubts as to the possibility of demonstrating a predisposition to retinal detachment by means of the ERG.

François and de Rouck also recorded the ERG on stimulation with blue light. They then obtained a lower b-potential than on stimulation with white light in patients with myopia or detachment of the retina. Similar observations were reported earlier by Queiroga (1953). In connection with an investigation by Henkes and Rottier (1953) I must, however, stress the difficulty of obtaining a sufficiently strong colored stimulus light. Consequently, there is a great risk of the decrease observed in the potentials being due to the use of too weak a stimulus light in an insufficiently dark-adapted eye.

I have made a few examinations with very strong blue light, the source of light being a photographic electronic flash. In patients with retinal detachment, the size of the b-potential was the same as in a clinical standard recording.

No other systematic investigations on the ERG in detachment of the retina have been published. The literature contains only scattered observations, reported in connection with various surveys of electroretinography and its clinical application (Queiroga, 1953; Burian, 1953) or preliminary reports (Karpe, 1948; François and Verriest, 1955).

Method

The electroretinographic examination was made according to the standardized method described by Karpe (1945, 1948, 1950). During the past five years, the ERG of both eyes has been recorded simultaneously.

The ERG was recorded, when possible, as soon as retinal detachment was diagnosed, at latest on the day of admission to the eye clinic. In some cases, in which the detachment decreased after a few days in bed, an additional ERG was made before operation. In those cases in which operation was successful, the ERG was recorded, whenever possible, some time after operation, usually two to three months later. In a few patients repeated recordings were made over a longer period (5 to 10 years).

As the normal material, a series collected by Zeidler (1956) was used. In this series, the refraction ranged from −0.75 D. to +2.5 D. (+3.5 D. in older persons).

Case Material

The case material comprises the 250 patients with detachment of the retina in

whom ERG's have been recorded at the Eye Clinic of Karolinska Sjukhuset up to the time of writing (April, 1956). The first patients were examined in 1944, and since 1950 an ERG has been made in practically every case of retinal detachment. Any selection of cases has been purely random.

Only those cases in which the diagnosis could be verified by ophthalmoscopy have been included. Since the earlier results (Karpe and Rendahl, 1952) were based on examination of adults (19 years of age and above), the few children examined have also been excluded from the present series. The reason why the younger age groups were not included is that no representative control material was available earlier for comparison.

The duration of the disease varied greatly. Some patients were examined postoperatively only, e. g., control cases from other departments of ophthalmology. In some of the patients not operated on, the ERG was recorded only to confirm the clinical examination.

Altogether, 250 patients were examined. Bilateral retinal detachment was present in 27 cases; the material thus comprises 277 eyes with retinal detachment. In 17 of these cases a recurrence took place later; the recurrences have not been included in the material but will be the subject of comment later in this paper.

From the etiologic point of view, the patients can be grouped as in Table 1. Initially, however, the material will be considered as a whole, after which a comparison will be made between the various groups.

Results

The ERG in Retinal Detachment.—In retinal detachment a subnormal or extinguished ERG is obtained. The latter applies when a large area is detached or in long-standing extensive detachment. The different types of ERG are shown in Figure 1.

Of the 277 eyes in the present series, a negative ERG was, however, present before operation in 8 cases. In all these cases another eye disease, e. g., retinitis proliferans, was present concomitantly. Eight other patients had a normal ERG of the eye with retinal detachment. In all these cases there was a small peripheral detachment, which was discovered by chance when the patient came to have his glasses changed. In one case the detachment was around a melanoma; the patient refused operation, and spontaneous healing occurred. In one case the detachment was post-traumatic, in one in conjunction with choroiditis, and in five cases the cause was unknown.

The size of the b-potential can suitably be used as a rough measure of retinal function. The range of normal variation has been studied at several clinics, but a direct comparison between different series is not always possible, owing to differences in the conditions of examination. Figure 2 shows the values in a normal series from Karolinska Sjukhuset with approximately the same sex and age distribution as the patients with retinal detachment (after Zeidler, 1956). The results of the ERG of eyes with retinal detachment are also recorded in the Figure. It is immediately evident that

TABLE 1.—*Classification of Cases According to Etiology*

Etiology	Eyes, No.	Comment
Idiopathic detachment	148	
Traumatic detachment	48	
Postoperative detachment	19	Cataract extraction; operation for glaucoma
Intraocular tumor	16	Malignant melanoma of choroid, 14 cases; carcinoma metastasis, 2 cases
Inflammation or allied conditions	42	Retinitis proliferans, 14 cases; periphlebitis, 5 cases; uveitis, 20 cases; diabetic retinopathy, 2 cases; hypertensive retinopathy, 1 case
Idiopathic? (during pregnancy)	4	No toxicosis or retinopathy

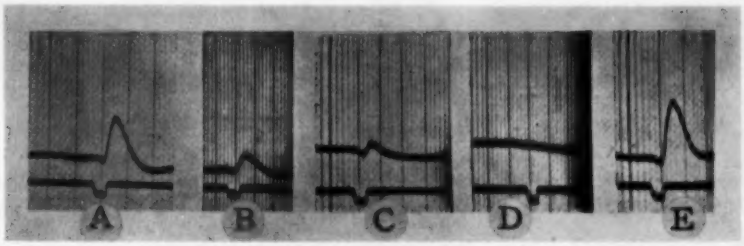

Fig. 1.—Normal and pathologic ERG's. Upper tracing, ERG; lower tracing, stimulus flash. Time marking: 0.1 and 0.02 seconds. *A*, normal ERG. *B*, subnormal ERG in a case of retinal detachment. *C*, negative ERG in a case of thrombosis of the retinal vein. *D*, extinguished ERG in a case of retinitis pigmentosa (this eye had good central vision). *E*, supernormal ERG in a case of acute glaucoma with visible venous stasis (the ERG became normal after the attack had subsided).

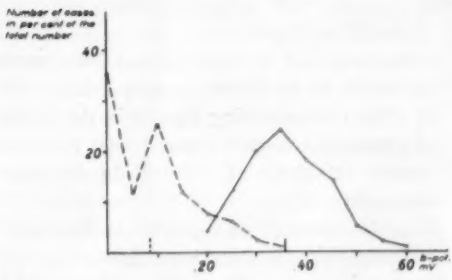

Fig. 2.—The association of retinal detachment with a subnormal b-potential. Comparison of the frequency distribution curve for the b-waves from 258 normal eyes (solid line) with that from 277 eyes with retinal detachment (broken line). The mean value for the normal b-potential is 0.36 mV., and that for the cases with retinal detachment is 0.09 mv.

retinal detachment is associated with a very marked decrease in the b-potential. Thus, the mean b-potential of 258 healthy eyes was 0.36 mv., and that of 273 eyes with retinal detachment, only 0.09 mv.

Moreover, a direct correlation exists between the size of the detached area and the size of the b-potential (Table 2).

It can be inferred from Table 2 that the decrease in the b-potential is, at least in part, directly dependent on the extent of detachment. It nevertheless seems as if some additional factor is also responsible for the size of the ERG. For example, in the group in which only one-fourth of the retina was detached, a b-potential as low as 0.05 mv. was recorded in some cases. It therefore seems likely that the ERG is also a measure of the functional capacity of the retina ("vitality").

The subsequent course in these 277 cases is shown in Table 3. In eight cases the results are unknown. Operation was at first successful in 17 patients, but a recurrence took place later. These cases, as well as the five in which spontaneous reattachment occurred, will be analyzed separately.

Of the remaining 247 cases, 144 were operated on. In 103 cases no intervention was made. To this category belong, for example, a large group of patients with extensive, long-standing detachment, who

TABLE 2.—*Relation Between Extent of Retinal Detachment* and Size of b-Potential (Mean Values)*

Area of Retina Detached	b-Potential, Mv.	Cases, No. †
One-fourth	0.18	41
One-half	0.11	96
Three-fourths	0.05	39
Whole	0.007	59

* The extent of the retinal detachment has been estimated in quadrants. On the basis of these data, a calculation has then been made of the percentage of the retina detached in the various groups of cases. These percentage figures are therefore to be regarded as highly approximative comparative figures, and only large differences have been accorded any definite importance. The mean area detached was 62%.

† The patients in whom no ERG was recorded preoperatively are not included.

TABLE 3.—*Survey of the Etiology, Treatment, and Results* *

Course	Etiology						Total
	Idiopathic	Traumatic	Postoperative	Tumor	Inflammatory	Pregnancy	
No operation	45 (16)	11 (1)	8 (3)	14 (2)	23 (6)	2 (1)	103 (29)
Unsuccessful operation	44 (23)	12 (5)	8 (2)	1 (0)	4 (0)	1 (0)	70 (30)
Successful operation	45 (25)	19 (8)	2 (0)	--	7 (2)	1 (1)	74 (36)
Spontaneous reattachment	1 (0)	1 (0)	1 (0)	1 (1)	1 (0)	--	5 (1)
Recurrence	10 (8)	4 (4)	--	--	3 (3)	--	17 (15)
Unknown†	3 (1)	1 (0)	--	--	4 (3)	--	8 (4)
Total	148 (73)	48 (18)	19 (5)	16 (3)	42 (14)	4 (2)	277 (115)

* The numbers in parentheses denote the number of myopes in each group.
† One dead, one address unknown, six in process of reattachment.

only made inquiries as to the possibilities of treatment.

Results of Operation.—Operation was performed with Larsson's method (1930, 1932), slightly modified. The tear is first surrounded by multiple diascleral diathermy cauterizations, made with a small ball electrode. The subretinal fluid is then emptied through a puncture made with a galvanocautery or Safar needle.

Reattachment took place in 74 of the 144 cases operated on. In 20 of the 70 cases in which operation was unsuccessful, the intervention had been made because of some disease of the other eye, despite the fact that the prognosis was regarded as poor.

If the ERG of the eyes in which operation was successful is studied, the b-potential is seen to be considerably higher than in cases in which operation was not successful. Thus, the mean b-potential in the former group (74 eyes) was 0.14 mv., and that in the latter (70 eyes), only 0.09 mv; the difference, 0.05 ± 0.015 mv., is significant.

This difference does not seem to be due to a difference in age or in refraction. The mean age in the former group was 44.6 years, and that in the latter, 48.3 years; the difference is not significant.

As far as the refraction is concerned, 39 of the patients in the former group were nonmyopic and 35 were myopic, the mean refraction in the latter category being -4.5 D. The corresponding figures in the group of unsuccessful cases were 39 and 31, with a mean refraction of -6.8 D. in the latter category.

In the operated on cases no demonstrable difference was present between the size of the b-potential in the myopes and in the nonmyopes. The mean b-potential was approximately the same, i. e., in the myopic patients 0.13 mv. in the successfully operated on cases and 0.09 mv. in the unsuccessfully operated on ones, the corresponding figures in the nonmyopes being 0.14 and 0.09 mv., respectively.

It is true that the average size of the detachment was somewhat greater in the group in which operation was unsuccessful, i. e., 52% as compared with 46%. However, as stated earlier, these figures are highly approximative, and such a small difference cannot be regarded as significant.

Consequently, it does not appear probable that the extent of detachment was responsible for the poorer results of operation in the latter group. The larger b-potential in the former group indicates that there was less severe damage to the retina in these cases. This implies that the ERG can be of some prognostic value in cases that are hard to evaluate.

The ERG After Reattachment.—It seems plausible to expect normalization of the ERG after a successful operation. However, even if an increase in the b-potential is seen in some cases, there is as a rule little improvement in the ERG, although the retina has reattached and function has been considerably improved as regards both visual acuity and visual field.

In the cases in which operation was successful, the mean b-potential before operation was 0.14 mv. The ERG was repeated postoperatively in 30 cases. At the first check-up (within one year of operation) the mean b-potential was 0.16 mv. A few patients (10 eyes) could be followed for a considerably longer time, the observation period ranging from 5 to 10 years. In these follow-up examinations, the mean b-potential was found to have remained unchanged, at 0.16 mv.

Several possibilities exist to explain the failure of a normal ERG to appear in an eye successfully operated on, but none of them can as yet be regarded as more than hypothetical (Karpe and Rendahl, 1952). For instance, with the operative technique used, the multiple cauterizations produce an area of damaged retina that is often almost as large as the original detachment, and this area may well fail to function normally. Moreover, the retinal and choroidal circulation are affected in the treated area, and this may greatly influence development of the electric potential. Another possibility is that the scars may form vertical connections through the various retinal layers and thus cause internal shunting of the normal difference between the potentials in them.

A deterioration in the ERG was recorded postoperatively in only three of the aforementioned cases. In a few cases an increased negativity can be seen during the first postoperative months (see Fig. 1), but it generally disappears later. This negativity can probably be ascribed to the retinal changes produced by operation. A similar increase in negativity is found in some other conditions associated with retinal damage, such as choroiditis, the initial stages of siderosis, methyl alcohol poisoning, and certain forms of thrombosis of the retinal vein.

The ERG of the Other Eye.—A question of great interest is whether or not a predisposition to retinal detachment exists. Thus, Karpe and Rendahl (1952) were able to show that the b-potential of the "healthy" eye in patients with retinal detachment was lower than that in the eyes of a normal series. At that time the case material was, however, too small to permit any further elucidation of this difference, but it was pointed out that the presence of myopia, for example, had to be taken into account.

François and de Rouck did, it is true, find a poorer ERG in their 26 cases of retinal detachment than in normal cases, but they stated that, in their series, this difference could be explained by the presence of myopia.

In the present series, a clinically "healthy" eye was found in 156 cases. In the remaining patients there was either bilateral detachment of the retina (27 cases) or some other disease (inflammation or allied conditions, glaucoma) and, in a few cases, impairment of vision due to cataract or to a severe error of refraction. In a few cases the recording was not fully satisfactory from the technical point of view and therefore was not included.

The mean b-potential of these 156 eyes was 0.29 mv. If the material is considered from the etiologic aspect, no definite difference is found between the group with idiopathic and those with traumatic detachment or detachment from other causes.

If, on the other hand, the cases are classified on the basis of the refraction, an interesting difference can be noted between the emmetropic and hyperopic patients (Group EH) and the myopic patients (Group M). Thus, the mean b-potential recorded in Group EH was 0.32 mv. (standard error, 0.01 mv.) and that in Group M was only 0.26 mv. (standard error, 0.01

mv.). The difference, 0.06±0.0144 mv., is significant.

If Group EH is compared with the aforementioned normal series, in which the mean b-potential was 0.36 mv. (standard error, 0.005 mv.), the difference, 0.04±0.011 mv., is also found to be significant.

We have not yet any representative control series for myopic eyes at Karolinska Sjukhuset, since the basis on which myopic eyes should be classified in such an investigation is highly doubtful. As François and de Rouck have recently stressed, the refraction is not a suitable basis for classification.

In order to have some material for comparison, I assembled a random series of myopic eyes from our ERG records. In most cases, however, the reason for examination was that malignant myopia was suspected or present or that the patient sought advice for symptoms which aroused a suspicion of retinal detachment. The mean refraction in this series (26 eyes) was −10.8 D., and the mean age, 40.2 years. The mean b-potential was 0.29 mv. (standard error, 0.018 mv.).

The difference between the mean b-potential in this series and that in Group M is 0.03±0.02 mv., i. e., it is not significant. Since the control series exhibited more severe myopia (and probably more advanced fundus changes) it is nevertheless probable that here, as well, there was a significant difference between the b-potential in this series and in the patients with retinal detachment.

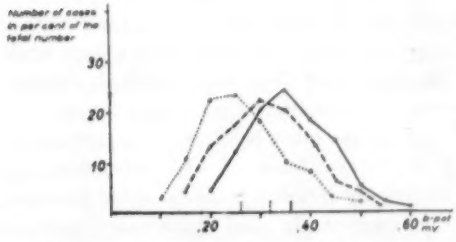

Fig. 3.—Comparison of the normal frequency distribution of the b-potential (solid line) with that of 85 nonmyopes with retinal detachment of the other eye (broken line, mean b-potential 0.32 mv.) and that of 71 myopes with retinal detachment of the other eye (dotted line, mean b-potential 0.26 mv.).

A graphic representation of these conditions is given in Figure 3. The frequency distribution curve of the myopic control series, which was not a representative selection, was also irregular and therefore has not been included.

As far as the ERG of the eye with retinal detachment was concerned, the mean value of the b-potential proved to be considerably higher in those cases in which operation was successful than in those in which it was unsuccessful. If the ERG of the other eye is studied in these two groups, the same difference is apparent. In the group in which reattachment took place, the mean b-potential was 0.34 mv. in the nonmyopic patients (21 cases) and 0.29 in the myopic ones (24 cases). The corresponding figures in the group in which operation was unsuccessful were 0.30 mv. (22 cases) and 0.23 mv. (18 cases). The material is too small to establish whether any significant difference exists, and it is still less possible at present to evaluate the relation of the prognostically favorable group to the normal series. As yet, the material must still be considered as a whole, while bearing in mind the aforementioned tendencies. The true conditions can be elucidated only by a study of a considerably larger series.

Finally, it is of interest to note the conditions in those cases in which there was an intraocular tumor with secondary detachment of the retina of the other eye, in which an entirely different pathogenetic

The largest group is that of idiopathic detachment. A comparison between these etiologic groups. I shall now give a more detailed account of the b-potential of the eye with retinal detachment in the various etiologic groups, with due reservation for the fact that certain of the subgroups comprise relatively few cases.

The ERG and the Etiology.—The material has hitherto been regarded as a whole. It was, however, pointed out in connection with the study of the "healthy" eye that it

was not possible to demonstrate any difference in this respect between the various mechanism can be envisaged. In these 11 cases, the mean b-potential of the other eye was 0.37 mv., but the material is obviously too small to permit any statistical analysis. cases and the collected material is given in Table 4. It is evident that no difference exists between the idiopathic group and the whole material.

TABLE 4.—*Comparison Between the ERG in Idiopathic Detachment and the ERG in All Cases of Retinal Detachment*

Idiopathic Detachment	Eyes, No.	Mean b-Potential, Mv.	Detached Area, %	Mean Age, Yr.
Nonmyopes	73	0.08	65	52.6
Myopes	75	0.09	57	48.4
Total	148	0.09	61	50.5
All cases	277	0.09	62	

If the groups of myopes and nonmyopes are studied, it is seen that the mean age was somewhat lower and the detached area less extensive in the former group. The difference is not significant, nor is the slightly higher b-potential in the group of myopes.

A comparison between the different etiologic groups with respect to the results of operation is shown in Table 5.

The next largest group is that of traumatic retinal detachment. A perforating injury had occurred in 9 of these 48 cases, and a blunt injury to the eye or its surroundings, in 39. In this group as well, no definite difference is found between the b-potential of the myopic and the nonmyopic eyes. If the ERG is considered in view of the operative results, it can be inferred from Table 5 that no difference exists in comparison with the total material.

The subgroups of traumatic detachment of the retina are small, but the results are in good agreement with earlier experience. The mean b-potential of the eyes in this category was, on the contrary, higher than in the collected material (0.12 mv. as compared with 0.09 mv.). This difference is, however, explained by the fact that the group contains such a large number of prognostically favorable cases (cf. Table 3).

The ERG in Spontaneous Reattachment

In a few cases, spontaneous reattachment or delimitation of the detachment took place. This group comprises only five cases, but the general impression is that the ERG was strikingly good in these patients (mean area detached, 40%; mean b-potential, 0.20 mv.).

The ERG in Recurrence of Detachment

Those cases have been denoted as recurrences in which the retina was evaluated as reattached, and the patient had, at least to a moderate degree, resumed his normal occupation before signs of a new detachment appeared. Thus, patients in whom the retina became detached during the course of postoperative treatment have not been included.

TABLE 5.—*Comparison Between the ERG in Idiopathic or Traumatic Retinal Detachment and the ERG in the Whole Material, with Special Reference to Results of Operation* *

Detachment	Operation Successful			Operation Unsuccessful		
	b-Potential Preop., Mv.	Detached Area, %	Cases, No.	b-Potential Preop., Mv.	Detached Area, %	Cases, No.
Idiopathic	0.14	49	44	0.09	53	37
Traumatic	0.14	46	17	0.09	50	9
All cases	0.14	46	74	0.09	52	79

* All values are mean values.

TABLE 6.—*The Course in Treatment of Recurrent Retinal Detachment* *

	Etiology			
	Idiopathic	Post-Traumatic	Inflammatory	Total
No reoperation	1	3 (3)	--	4
Unsuccessful reoperation	5 (4)	--	3 (3)	8
Successful reoperation	4 (4)	1 (1)	--	5
Total	10	4	3	17

* The figures in parentheses denote the number of myopes in each group.

The group comprises 17 patients, 15 of whom were myopes. The etiology is shown in Table 3, and the course, in Table 6.

The mean area of the retina primarily detached was 48% in these patients, and the mean b-potential, 0.12 mv. It is true that this value is slightly lower than the mean value in the prognostically favorable cases in the whole material (0.14 mv.), but the difference is not significant. The mean b-potential of the other ("healthy") eye of the myopes was 0.29 mv.

The ERG of Eyes with Later Detachment.—The way in which the b-potential decreases with the occurrence of retinal detachment is well illustrated by seven cases in which the ERG was recorded before this event. In the majority (five cases) the recording had been made in connection with examination for detachment of the retina of the other eye, whereas two patients were examined before extraction of a cataract (uveitis with complicating cataract and senile cataract, respectively). At the first recording, the mean b-potential in these seven patients (six myopes) was 0.25 mv. At the later examination, on the appearance of retinal detachment, the mean value had fallen to 0.12 mv., the average size of the detached area being 47%. Four of the patients were operated on with success, and one, unsuccessfully.

It is thus evident that a considerable deterioration takes place in the ERG with the appearance of retinal detachment. In two of the cases only a few months had elapsed between the two recordings, and in one case the interval was only three days.

On the other hand, it is not found that the ERG of these eyes was poorer at the first examination (0.25 mv.) than that of the other, "healthy," eye in the collected material (0.26 mv.).

Comment

In clinical electroretinography, the size of the b-potential is a measure of the "functional capacity" of the retina; consequently, it decreases if only part of the retina functions, or if the whole retina functions but to an impaired degree (Granit, 1947, 1955; Karpe and Rendahl, 1952).

In retinal detachment a considerably reduced b-potential is, in fact, obtained, and the deterioration of the ERG seems to depend mainly on two factors: the extent of the detachment and the "vitality" of the retina. The latter is evident from the fact that the mean b-potential is distinctly higher in those patients in whom operation is successful than in those unsuccessfully operated on. These observations are statistically significant, but the great individual variations make it difficult to assign any particular case to a certain prognostic group. The ERG must nevertheless be regarded as of great importance in retinal detachment, when it is necessary to decide in a case that is hard to evaluate whether or not operation is to be recommended. A relatively good ERG is especially valuable when it is intended to suggest operation in a case in which other clinical data argue against the intervention.

Of particular interest is the observation that patients with retinal detachment have a poorer ERG of the other, clinically healthy, eye than that of normal persons. This fact was already pointed out earlier

by Karpe and Rendahl (1952), but the case material was then so small that the impormaterial that this observation is statistically tance of myopia could not be determined. It is evident from the present collected case significant as far as nonmyopic eyes are concerned and that this probably applies to myopic eyes as well. Representative control material for the latter category is, however, lacking.

It also appears probable that the deterioration in the ERG of the "healthy" eye of patients with retinal detachment is less in cases in which operation is subsequently successful. The case material is, however, as yet too small to permit any statistical analysis of this matter.

It therefore seems evident that a predisposition to retinal detachment exists in these patients. This fact has long been stressed on the basis of clinical data, but it has now been possible to verify it electroretinographically.

Mention may also be made of the following situation. In a small group of patients in whom retinal detachment was caused by an intraocular tumor, an entirely different pathogenetic mechanism must be envisaged. In these cases, the b-potential of the clinically healthy eye was, in fact, normal.

To sum up, it can be stated that the present investigation on 277 eyes has been able to verify the conclusions based on the earlier case material (Karpe and Rendahl, 1952). It has also been possible to confirm electroretinographically the existence of a predisposition to retinal detachment in the form of a deteriorated ERG ("retina with poor vitality"). In addition, it has been shown that this tendency to retinal detachment is present in both eyes of such patients and in both myopic and nonmyopic eyes.

Summary

The clinical electroretinogram (ERG) has been studied in 277 eyes with retinal detachment (250 patients). Statistical analyses of the results show (1) that, as expected, the b-potential decreases in relation to the area of detachment; (2) the mean b-potential before operation is higher in those eyes in which operation is later successful; (3) the b-potential of the other, "healthy," eye of these patients is lower than that in a normal person, this difference also being present in nonmyopic eyes.

The aforegoing observations apply regardless of whether detachment is idiopathic or traumatic.

The results seem to confirm the existence of a predisposition to retinal detachment and that a poor ERG is generally associated with a poor prognosis.

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Announcement

The American Board of Ophthalmology is not accepting any applications at this time for the proposed examination in ophthalmic surgery. Plans are being formulated, and it may be some time before anything definite is done. Please watch for further announcements in the ophthalmic journals. More definite information will be sent to all diplomates by the Board office when plans are completed.

Dr. Merrill J. King, Secretary
American Board of Ophthalmology
56 Ivie Road
Cape Cottage, Maine

Development of Immunity by Repeated Infection of Trachoma

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It has been accepted in general that there is a relative immunity in trachoma associated with persistence of the infection but that there is no permanent immunity. Reinfection experiments in man as well as in monkeys have resulted in an onset of trachoma without exception.[1-3] Superinoculation experiments, however, have not always resulted in a provocation of the symptoms.[4] Vaccine has been tried in the treatment of trachoma without benefit.[5] Some serological activity has been demonstrated in trachoma patients.[6,7] But γ-globulin in the patient's serum[8] and in the infected conjunctival tissue[9] did not show significant increase. A toxin-like substance of trachoma virus and the allergic nature of it have been demonstrated experimentally.[10] Some allergic tissue reaction was demonstrated histologically in the trachoma-infected tissue.[11] Some other workers still claimed the presence of immunity in trachoma, either of congenital or of acquired origin.[12]

The recent advance in the treatment of trachoma with antibiotics has shortened the course of the disease considerably, and, consequently, we have been able to conduct repeated experiments of trachoma reinfection in a relatively short period of time. Such an experiment should give some indication of the immunity and allergy problem in trachoma.

The preliminary report of this work was published by one of us (J. T.) in 1953 on the five-times-repeated infection on his own eyes.[13] After that, more inoculation experiments were added, and the work has been completed after an observation period of five years.

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Details of Repeated Infections

Donors.—The material was obtained from the patient with acute or chronic trachoma with a great number of inclusion bodies. These cases were sometimes natural trachoma and sometimes experimental cases.

Subjects.—All four of us, three nurses, and Mrs. Tsutsui volunteered to be the subjects.

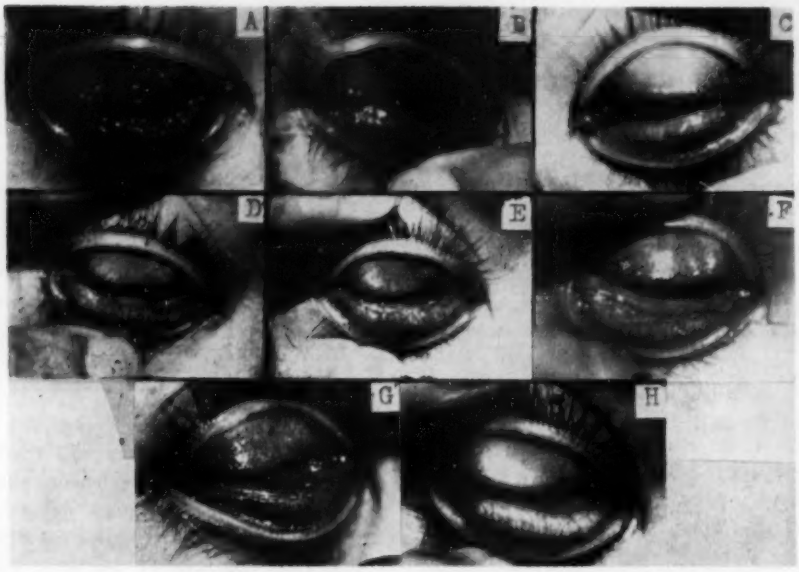
Method of Inoculation.—Scrapings from the donors were rubbed into the conjunctiva of the volunteers. Possible contamination with bacteria was prevented by application of a weak solution of penicillin and streptomycin topically for three to four days after the inoculation.

Reinfection.—After the onset of the disease by the previous inoculation, the course was followed for a certain period of time. Then the case was treated with antibiotics. After a complete cure was obtained, a reinfection experiment was performed with the same technique as in the previous inoculation. In some experiments, spontaneous cure was observed for a long period of time.

Method of Indicating Inclusion Bodies.—The rate of inclusion bodies was indicated in percentages. The number of cells with inclusion bodies were divided by the number of epithelial cells which were examined microscopically.

Report of Cases

CASE 1 (J. T.) (Table, Fig.).—The first inoculation was performed in the right eye



Change of the eye manifestations following repeated infection of trachoma. *A*, the 1st inoculation experiment; *B*, the 2d inoculation experiment; *C*, the 3rd inoculation experiment; *D*, the 4th inoculation experiment; *E*, the 5th inoculation experiment; *F*, the 7th inoculation experiment; *G*, the 10th inoculation experiment; *H*, spontaneous cure two months after the 10th inoculation experiment.

on Dec. 13, 1951. The disease occurred with acute symptoms on the 11th day after inoculation. Acute follicular conjunctivitis with lid edema and preauricular adenopathy developed in a few days. The rate of inclusion bodies reached 3.9% on the 10th day. From the 10th day of the disease, treatment with oxytetracycline (Terramycin) was started and continued for 2 weeks, until the cure was complete. No relapse was seen after six months.

The second inoculation was made in the right eye on July 31, 1952. After a five-day incubation period, the disease occurred more quickly than in the first infection, with the manifestation of intensive acute follicular conjunctivitis. But less intensive lid edema and preauricular adenopathy were recognized. The number of inclusion bodies reached its maximum value, of 3.1%, on the 22nd day of the disease. Oxytetracycline treatment was started on the 22nd day and was given for 20 days, until the cure was complete.

The third inoculation was made in the left eye on Aug. 27, 1952. After three days' incubation, the disease occurred more quickly but less intensively than before, with the manifestations of acute follicular conjunctivitis. The lid edema and preauricular adenopathy were also less intensive. The rate of inclusion bodies reached its maximum, of 0.61%, on the 11th day. Oxytetracycline treatment was begun on the 17th day and was needed for 25 days, until cure was complete.

The fourth inoculation was made in the right eye on Oct. 6, 1952, but after the inoculation the typical trachoma affection did not appear during one month. No inclusion bodies were found.

The fifth inoculation was made in the right eye on Nov. 6, 1952. After three days' incubation, the disease occurred more slowly and less intensively than the previous infections. A smaller number of follicles and moderate proliferation of papillae could be found during the whole course. Lid edema

Relation Between Repeated Infection of Trachoma and Clinical Findings

Inoculation No.	Inoculation Side*	Inoculation Date	Incubation Period, Days	Duration of Disease, Days†	Acuteness of Onset	Preauricular Adenopathy	Lid Edema	Hyperemia of Conjunctiva	Chemosis	Follicles	Papillae	Discharge	Epithelium with Inclusion Bodies, % (Max. Value)
Case 1 (J. T.)													
1	R (1)	12/13/51	11	10	++	+	+++	+++	+++	+++	±	+++	3.9
2	R (2)	7/31/52	5	22	+++	±	+	++	+++	+++	±	++	3.1
3	L (1)	8/27/52	3	17	+++	±	±	++	++	++	+	+	0.61
4	R (3)	10/ 6/52	–	0	–	–	–	–	–	±	–	–	0
5	R (4)	11/ 6/52	3	23	+	–	–	+	±	+	+	–	0
6	L (2)	12/30/52	3	34	±	–	–	+	–	+	+	–	1.9
7	R (5)	2/ 4/53	6	105	±	–	–	+	–	±	+	–	0.4
8	R (6)	9/ 3/55	4	30	+++	+	+	+++	++	++	++	+++	0.4
9	L (3)	3/ 3/56	3‡	3 mo. for spontaneous cure	++	–	+	++	+	+	++	++	0.09
10	R (7)	5/ 4/56	3‡	1 mo. for spontaneous cure	+	–	–	++	–	+	++	++	0
Case 2 (T. F.)													
1	L (1)	10/ 2/52	5	5	++	±	+++	+++	++	+++	±	+++	1.1
2	R (1)	10/17/52	12	9	+++	–	–	++	+	++	±	++	2.1
3	L (2)	12/15/52	6	10	+	–	–	++	+	++	+	+	1.7
4	R (2)	3/ 9/53	3	14	+	–	–	++	+	+	+	–	1.3
Case 3 (S. T.)													
1	L (1)	9/23/52	5	10	++	±	++	+++	+++	+++	±	+++	4.5
2	L (2)	10/24/52	3	10	++	–	+	++	++	++	±	++	4.5
3	L (3)	1/14/52	3	7	++	–	–	++	+	++	±	+	1.7
4	L (4)	5/ 9/53	3	3	++	–	–	++	+	++	±	+	Not examined
	R (1)	5/ 9/53	3	3	++	–	–	++	+	++	±	+	Not examined

* The number of the inoculation on the side mentioned is given in parentheses.
† Duration of the disease before beginning of treatment.
‡ Direct reaction against the inoculum appeared a short time after the inoculation.

and preauricular adenopathy did not appear at all. Inclusion bodies could not be found at any time during the whole course.

The control inoculation was made at the same time as the fifth inoculation. The same inoculum as was used for the fifth inoculation was applied to another person who had never suffered from trachoma (subject: Mrs. T.). After three days' incubation, typical acute trachoma appeared and inclusion bodies were found.

The sixth inoculation was made in the left eye on Dec. 30, 1952. After three days' incubation, the disease occurred very gradually and mildly, so that, without careful observation, the onset could have been overlooked. Moderate proliferation of papillae and slight congestion were found mainly. The subjective symptoms were very slight. The maximum of inclusion bodies was 1.9%, on the 11th day. Oxytetracycline treatment was started on the 34th day and was given for two months, until the cure was complete.

The seventh inoculation was made in the right eye on Feb. 4, 1953. After six days of incubation, the disease occurred very gradually and mildly, as in the sixth inoculation. A moderate proliferation of papillae and a small number of follicles appeared. The manifestation was similar to a case of slight chronic trachoma. During 105 days the manifestation never become serious. The rate of inclusion bodies was 0.4% at their maximum, on the 85th day.

The eighth inoculation was made in the right eye on Sept. 3, 1955. The interval from the previous inoculation experiment was 28 months. The disease occurred with acute intensive symptoms on the fourth day. The manifestation of acute follicular conjunctivitis with lid edema and preauricular adenopathy developed in a few days. These symptoms were almost the same as those of the primary infection, but the incidence of inclusion bodies was very low. The maximum rate of inclusion bodies was only 0.4%, at the 10th day. Tetracycline (Achromycin) treatment was started on the 30th day and was given for 2 months, until the cure was complete.

The ninth inoculation was made in the left eye on March 3, 1956. Two hours after the inoculation, congestion and swelling of the conjunctiva appeared and lasted about ten hours. These irritative symptoms were only temporary and decreased in the following day. On the third day, the conjunctival inflammation occurred again and developed to typical acute follicular conjunctivitis. This intensive manifestation lasted about two weeks and then diminished gradually. Follicles had disappeared at the end of one month, and finally the disease healed spontaneously without any treatment. Maximum rate of inclusion bodies was 0.09% at the sixth day.

The 10th inoculation was made in the right eye on May 4, 1956. Thirty minutes after the inoculation, irritative symptoms of the conjunctiva started and developed to acute catarrhal conjunctivitis on the first day. The manifestation diminished temporarily on the following day, but follicles appeared on the third day. Typical acute follicular conjunctivitis lasted one week, and then the intensity decreased gradually. The cure was complete after one month, without any treatment. Inclusion bodies never appeared during this period. On the seventh day, inoculum was collected from this eye and inoculated into the right eye of Mrs. M., who is a nurse of the eye clinic. This eye was carefully observed day by day, but the disease never appeared during the following three months. A control experiment against the 10th inoculation experiment was made on S. T.'s right eye. The same inoculum which was used in the 10th inoculation was inoculated on May 4, 1956. No irritative symptoms appeared on the first day. After seven days of incubation, disease occurred with a manifestation of typical acute follicular conjunctivitis. There were inclusion bodies.

CASE 2 (T. F.) (Table).—The first inoculation was made in the left eye on Oct. 2, 1952. After five days' incubation, the

disease occurred with the manifestation of acute and intensive follicular conjunctivitis, which is characteristic in acute trachoma. Moderate lid edema and preauricular adenopathy were recognized. The rate of inclusion bodies reached its maximum, of 1.16%, on the fifth day. On and after the 5th day, oxytetracycline was applied, and it was given for 20 days, until the cure was complete.

The second inoculation was made in the right eye on Oct. 17, 1952. After 12 days' incubation, the disease occurred with the manifestation of typical acute trachoma. But lid edema and preauricular adenopathy could not be found. The rate of inclusion bodies reached its maximum, of 2.1%, on the 10th day. Oxytetracycline treatment was given for 20 days, until the cure was complete.

The third inoculation was made in the left eye on Dec. 15, 1952. After six days' incubation, the disease occurred less intensively than before, with subacute symptoms. The rate of inclusion bodies reached its maximum, of 1.7%, on the 10th day. Oxytetracycline treatment was needed for one month, until complete cure.

The fourth inoculation was made in the right eye on March 9, 1953. After three days' incubation, the disease occurred and developed with a nearly the same condition as in the third infection. Carbomycin (Magnamycin) treatment started on the 14th day and was given for 2 months, until the cure was complete.

Case 3 (S. T.) (Table).—The first inoculation was made in the left eye on Sept. 23, 1952. After five days' incubation, the disease and number of inclusion bodies detypical acute trachoma. But, in this case, preauricular adenopathy could not be found. The rate of inclusion bodies reached its maximum, of 4.5%, on the 10th day. Oxytetracycline treatment was applied from the 10th day and was needed for 20 days, until the complete cure.

The second inoculation was made in the left eye on Oct. 24, 1952. After three days' incubation, the disease occurred with the manifestations of intensive acute trachoma. The rate of inclusion bodies reached its maximum, of 4.5%, on the 10th day. Oxytetracycline treatment was applied from the 10th day and was given for 20 days, until the cure was complete.

The third inoculation was made in the left eye on Jan. 14, 1953. After three days' incubation, the disease occurred with rather mild manifestations. The subjective symptoms were less intensive than in the previous infections. The rate of inclusion bodies reached its maximum, of 1.7%, on the second day. Oxytetracycline treatment was given for 20 days, until the cure was complete.

The fourth inoculation was made in both eyes on May 9, 1953. The left eye had its fourth infection and the right eye had its primary infection. After three days' incubation, the attack of both eyes began simultaneously with the same intensity. The manifestations were more intensive in the left eye than in the right eye. The influence of repeated infection, however, was never felt in the left eye. The rate of the inclusion bodies was not examined. Oxytetracycline treatment was started on the third day and was continued for 20 days, until the cure was complete.

Effect of Immune Serum of Trachoma in the Acute Case

In the experiments of repeated infection of trachoma, the more often the infections were repeated the more the intensity of the disease and number of inclusion bodies decreased. This phenomenon seemed to be the result of an immunity caused by repeated infections. The therapeutic effect of immune serum on acute trachoma was examined.

Effect of Immune Serum on Acute Experimental Trachoma

Case 1 (H. M., laboratory technician).—This case was an acute experimental trachoma which broke out on the fifth day

after the onset. Immune serum was obtained from J. T. (Case 1 of repeated infection), who had had experimental trachoma five times at that time. The instillation of immune serum was performed every hour during the daytime and suspended for seven hours at night. After 24 hours of treatment, the discharge of the eye was diminishing remarkably. On the third day of treatment hyperemia of the bulbar conjunctiva nearly disappeared and many follicles began to dissolve. Inclusion bodies could not be demonstrated. On the fifth day the follicles nearly disappeared and the conjunctival capillaries again appeared normal. On the seventh day the symptoms became worse and the inclusion bodies appeared again. On the ninth day the disease became a typical case of acute trachoma.

Case 2 (Y. K., nurse of eye clinic).—This case also was an experimental acute trachoma, which broke out on the second day after the onset. The same immune serum was instilled repeatedly, as in the first case. After 24 hours of instillation the discharge of the eye diminished remarkably. On the third day after treatment almost all of follicles disappeared and the conjunctival capillaries appeared again. On the sixth day the symptoms nearly disappeared, and the instillation of serum was suspended on the seventh day. But a relapse occurred on the eighth day, and further instillation of the serum was ended, without benefit.

Case 3 (Mrs. T., control case).—This case also was an experimental acute trachoma, which broke out on the third day after the onset. The serum of a healthy person who had never suffered from trachoma was applied repeatedly. But no improvement of the manifestation was seen during seven days' instillation.

Effect of Immune Serum on the Attack of the Disease

Immune serum seemed to be slightly effective in acute trachoma. In the next experiment the effect of immune serum in the incubation period of the disease was examined.

Case 4 (K. H., nurse of eye clinic).—Two hours after inoculation of trachomatous material, the instillation of serum was begun. The immune serum, which was the same one as in Case 1, was instilled in the right eye, and the serum of a healthy person was instilled in the left eye. The frequency of instillation was same as in Case 1. On the third day the left eye was attacked; instillation of control serum was stopped, and oxytetracycline treatment was started. The instillation of immune serum was continued, but the disease occurred on the 10th day. The immune serum seemed to prolong the incubation period for one week. No difference was recognized in the symptoms of the two eyes.

Comment

In the experiment of repeated infection of trachoma, the most important problem was to know whether the inoculation had been made after complete cure of the previous infection or not. In a disease like trachoma, which continues with slight manifestations for a long time, it is very difficult to decide the time of cure. The relapse was watched without treatment for two months after the main trachomatous symptoms had disappeared as a result of treatment. If the duration of observation without treatment was shortened and the next inoculation was made within one month after the disappearance of clinical findings, the attack did not occur (see the result of fourth inoculation in Case 1). This might be superinoculation, and the other cases seemed to be reinfection.

In the serial inoculation experiments, immunological and allergic influences were carefully observed. In the first several infections, the more the infections were repeated the quicker the speed of attack became. This phenomenon seems to be due to the fact that the allergic reaction takes place more and more easily. After the third or fourth infection the intensity of an attack became less severe, and finally the disease occurred very mildly. This phenomenon

seems to be due to relative immunity to trachoma. But complete immunity could not be found. For the diminution of the intensity of the disease, the duration of each infection must be longer and the infection must be repeated. However, if the interval of two infection experiments is relatively long, the immunity phenomenon is reduced but the allergic influence is still left. Increased sensitivity of the conjunctiva to the trachoma virus or its toxin lasted for a relatively long time. For instance, in the last two inoculation experiments of the first case the conjunctival inflammation occurred within a very short time, approximately 30 minutes, but in the control case the incubation period was 7 days. Such an extreme difference of incubation period clearly is related to the hypersensitivity or allergic nature of the reaction induced by the trachoma virus. Some authors mention that tests using skin reaction to trachoma antigen are unsatisfactory but that observation of conjunctival hypersensitivity reactions seems to be more accurate.

The influence of repeated infection of trachoma on the incidence of inclusion bodies was also interesting. The inclusion bodies diminished in proportion to the repetition of the infection. The longer the duration of an attack is, the more remarkable is the influence on the diminution of the inclusion bodies. It is considered that if a subject is affected by trachoma for a long time the proliferation of trachoma virus becomes difficult. This phenomenon may be a part of immunity. In the natural case of trachoma, usually the same phenomenon is observed, and most cases of chronic trachoma reach a low virus condition. Moreover, the possibility of spontaneous healing of trachoma has been satisfactorily considered.

Is the trachoma immunity local or general? A satisfactory conclusion could not be obtained from these experiments, but some facts seem to be clear. The general immunity is more remarkable than the local immunity. The immune serum of a person who had received repeated infections could slightly control the disease in the incubation period or in the beginning of the disease. Another piece of evidence in connection with general immunity has been indicated. In Case 1 of repeated infection, the disease affected, in order, the right, right, and left eye. During the third infection, the left eye showed less intensive symptoms than in the previous infection. In Case 3 of repeated infection the fourth infection occurred in both eyes at the same time. Up to that time, the left eye had suffered from trachoma as often as four times but for the right eye it was a primary infection. However, in spite of the difference of frequency, the condition of the disease did not differ in the two eyes. If local immunity were more remarkable than general immunity, the manifestation of the left eye would have been less intensive than that of the right eye.

Many ophthalmologists believe that the onset of trachoma begins with a mild and chronic condition. Some authorities, however, believe that the onset of trachoma is always sudden. In this research, 26 eyes were inoculated and 24 eyes were affected. Twenty eyes were attacked with the acute intensive manifestation of trachoma, but four eyes were attacked with mild and chronic conditions. All of these four cases were extraordinary cases. They were fourth to seventh infections and never included the primary infection. Except these extraordinary cases, trachoma in this experiment always began with the acute manifestations.

Summary and Conclusion

The immunological and allergic nature of trachoma was observed in serial inoculation experiments. An immunity phenomenon could be demonstrated in diminution of the number of inclusion bodies and in the diminution of intensity of the disease during the repeated infection experiments. The diminution of intensity of the disease was found only when the repeated inoculations were made at relatively short intervals. If the interval of two inoculations was more

than two years, only hypersensitivity of the conjunctiva to the trachoma virus remained. In such a condition, the inoculation produced a rapid development of intensive allergic reaction of the conjunctiva, but the proliferation of virus was disturbed. In a certain case of repeated infection, spontaneous cure was found in a few months following acute intensive experimental trachoma.

The instillation of trachoma immune serum showed a partial therapeutic effect in acute trachoma, but the effect was not enough to cure the disease. The immunity of trachoma is not complete enough to prevent the disease, but it seems to be beneficial for the spontaneous cure of the disease.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted, and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest, and be accompanied with photographs whenever possible.

Unusual Ocular Involvement in Acute Lymphatic Leukemia

The occurrence of a severe ocular sign observed as the first evidence of a fatal systemic disease is here recorded.

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Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

The patient, a 15-month-old boy, was admitted to the National Institute of Allergy and Infectious Diseases with external ocular appearance as shown in Figure 1.

Pertinent history details include evidence of good general health until three weeks before admission, when rhinorrhea and coryza

Fig. 1.—Appearance of face and eyes of patient at time of initial ophthalmic examination (12 days after onset of ocular symptoms).

developed, which were progressive in severity and did not respond to local therapy.

Twelve days before admission the parents noted swelling and redness of the lower palpebral conjunctiva of both eyes. This progressed during the next seven days and was not influenced by local applications of chlortetracycline (Aureomycin) and of hydrocortisone ointments.

Five days before admission continued progression of the lower conjunctival swelling produced prolapse of the membrane and mechanical ectropion, bilaterally. This, plus increasing severity of upper respiratory congestion, prompted admission to a local hospital. Blood studies revealed a hemoglobin level of 14 gm. and leukocytosis, with a count of 24,000/cu. ml., of which 61% were lymphocytes. Treatment for 24 hours with systemic chlortetracycline and hydrocortisone was ineffectual. After four days the onset of definite respiratory distress motivated transfer of the patient to the Institute for further care.

Examination at this time showed the child to be well-developed and well-nourished. Positive physical findings included an extreme swelling and prolapse of the lower palpebral conjunctiva, as shown in Figure 1. The bilaterally exposed membranes were free of discharge, dark red, and without evident bleeding. Palpation disclosed the subconjunctival masses to be firm and nonreducible. Motility of both eyes was severely limited in all fields of gaze, especially downward. On examination of the cornea, anterior segment, and fundus, a suspect pallor of the peripheral retinae was observed. The appearance of exophthalmos was caused by anterior displacement of the lids and palpebral conjunctivae.

Swelling of the gingivae, hard and soft palate, and uvula was associated with an obvious embarrassment of the respiratory airway.

Examination of the chest gave the impression of dullness, without rales, at the left base. Cardiac size and action were normal.

On abdominal examination an enlarged liver and spleen were palpated at 1.5 and 2 cm., respectively, below the costal margins.

Palpable lymphadenopathy was noted at the preauricular and postauricular level and also in the anterior cervical, axillary, inguinal, and femoral regions. A firm 4 mm. swelling of the lower left thigh was slightly tender.

Roentgenographic studies indicated presence of left pleural effusion, plus hilar adenopathy and parenchymal infiltration, also on the left side. Skull films were normal, except for an impression of acute maxillary sinusitis and incomplete nasopharyngeal obstruction. Destruction of cortex of the distal left femur shaft was easily seen on films of that area.

The hemogram disclosed a hemoglobin value of 13.7 gm.; platelets, 293,000, and leukocytes, 50,000, of which 43% were lymphocytes, 27% neutrophils, 4% eosinophils, and 26% abnormal immature cells.

The diagnosis of acute leukemia, lymphatic type, was confirmed by bone marrow smears studied on the second hospital day. Sections of tissue removed in a subsequent biopsy of the left lower palpebral conjunctiva are shown in Figures 2A, 2B, and 3; there was dense infiltration by abnormal monocytic and lymphoblastic cells.

Treatment of the prolapsed membranes was local and palliative, including ice compresses, petrolatum gauze dressing, subconjunctival hyaluronidase injection, and instillation of sodium sulfacetamide, 30%.

Transfer of the patient to the National Cancer Institute was made to permit systemic treatment with the antimetabolites 6-mercaptopurine and 4-amino-N^{10}-methylpteroylglutamic acid (amethopterin). These substances were given daily for two weeks, in conjunction with hydrocortisone administered orally for 14 days. During this period a remarkable remission of ocular signs was noted, and this was correlated with reduction of the leukocyte count to normal levels. Figure 4 depicts the appearance of the patient one week after comple-

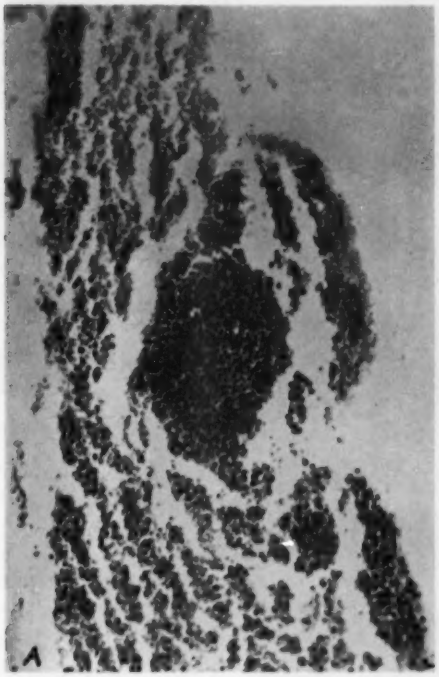

Fig. 2A.—Low-power magnification of conjunctival biopsy section, showing dense infiltration of lymphoblastic elements.

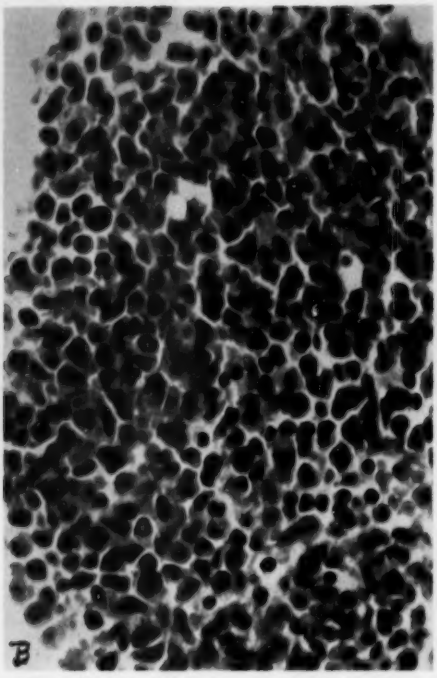

Fig. 2B.—High-power magnification of conjunctival biopsy specimen.

tion of this course. A transient episode of scrotal, conjunctival, and oral Monilia infection was controlled by local applications of methylrosanaline chloride (gentian violet).

The patient was discharged on the 34th day and placed on a maintenance level dosage of antimetabolite therapy.

After 47 days of outpatient observation, a recurrence of coryza, hoarseness, right conjunctival swelling, and bone pain prompted readmission.

Bone marrow studies at this time showed an almost complete replacement of the marrow by abnormal lymphoblastic cells.

Features of the subsequent clinical course were attributed to leukemic infiltration of the brain. These included frequent Jacksonian seizures and left-sided rigidity. The terminal course was complicated by a Pseudomonas septicemia which was not controlled by antibiotic therapy. The patient died on the 31st day of his second Institute admission. Figure 4 shows the extensive infiltration of the choroid observed on section of the right eye.

Comment

This patient displayed an unusual relationship between leukemia and conjunctival lymphomatous disease. The occurrence of leukemia in the course of any discrete lymphomatous lesion is known to be very erratic.[8,9] In the case of conjunctival lesions, the identification with lymphatic leukemia is made much more difficult by the frequent occurrence of either entity alone, especially because, when they are related, the interval between the onset of the two is subject to extreme variation. Early and recent reports bear out, first, that there is a paucity of such cases and, second, that the ocular lesion usually preceeds onset of leukemia.

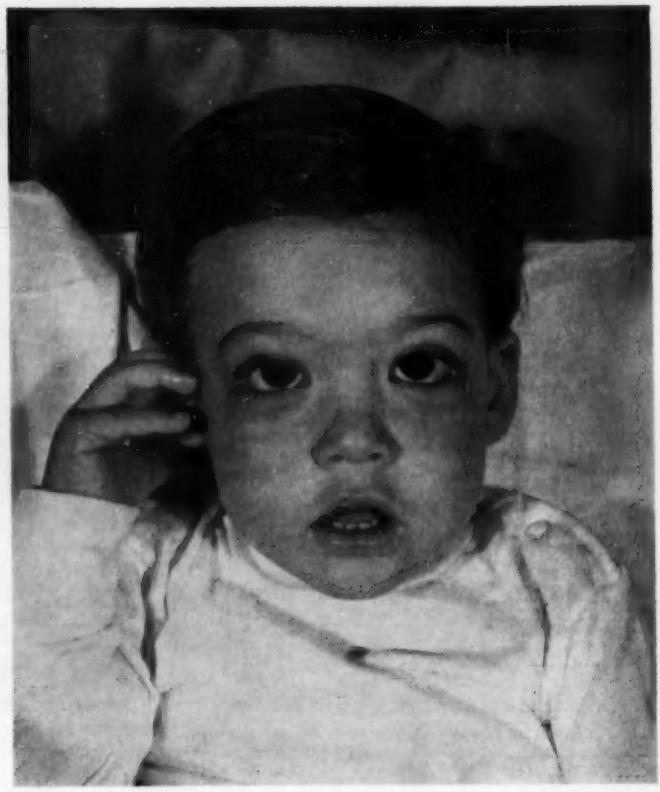

Fig. 3.—Appearance of patient one week after completion of 17-day course of systemic antimetabolite and hydrocortisone therapy.

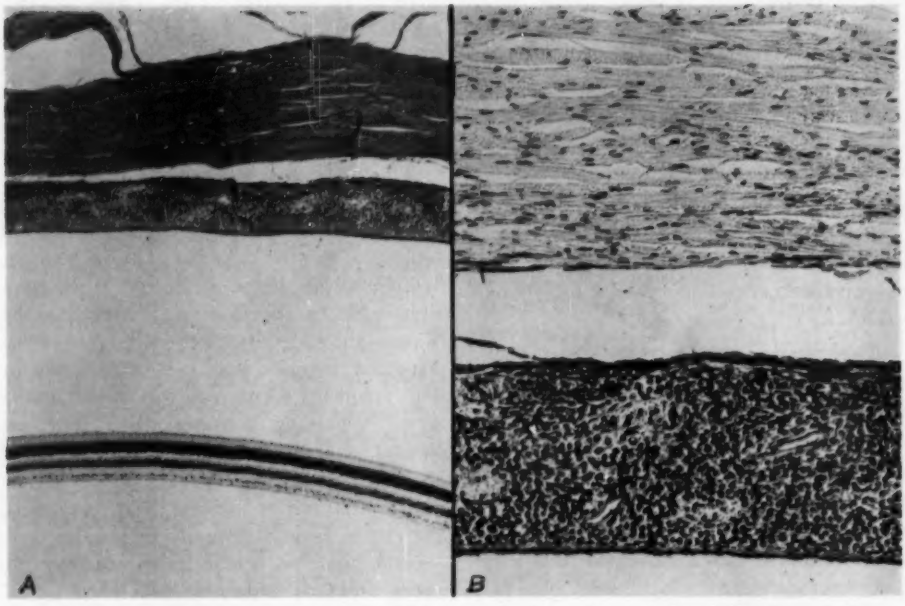

Fig. 4.—*A* (low power) and *B* (high power) show the extensive infiltration of the choroid by leukemic cells.

Becker Arnold[1] is credited with the first case report of a conjunctival lymphoma (1872), and the first clinical association of this lesion with lymphatic leukemia was reported by Leber[2] six years later. The patient had dense infiltration of the conjunctiva beneath all four lids, of one year's duration, and succumbed to the blood dyscrasia three months later. Subsequent to this, Axenfeld[3] mentioned four additional cases of lymphomatous infiltration of the lids in which leukemic changes were noted either in vivo or at autopsy. Löwenstein[4] in 1918 recorded an instance of bilateral lymphomas of the bulbar conjunctiva, which recurred within one year of excision and were associated with death from leukemia four years later.

A conjunctival lesion as the presenting sign of lymphatic leukemia was next reported by Reese and Guy[5] in 1933. This patient, a 69-year-old white man, displayed a unilateral mass of the bulbar conjunctiva associated with exophthalmos and leukocytosis. Saradarian's[6] case report of 1940 more nearly resembles the features of our own case: It concerned a 60-year-old white man whose bilateral conjunctival swellings preceded death from leukemia by only three weeks. McGavic[7] has recently added to his initial excellent study a 16-year follow-up of 20 patients with ocular lymphoma. Ten of this group have died of lymphomatous disease, two with definite leukemia.

The foregoing report of a case of leukemia in a 15-month-old white boy represents the most recent example of an association between conjunctival lymphoma and fatal leukemia. We feel that it is exceptional in relation to the cases reviewed because of its severity, symmetry, early age of occurrence, and proximity of onset of the conjunctival lesion to that of fatal leukemia.

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Embryotoxon with Associated Hemangioma of the Globe

Embryotoxon [1] has been described under numerous names, such as arcus juvenilis, congenital hyaline membranes of the posterior surface of the cornea,[2] noninflammatory congenital opacities,[3] and posterior marginal dysplasia of the cornea.[4] Each of these terms, however, has been shown to be lacking in either a complete or an accurate description of the glassy ring-like structures at the periphery of the posterior surface of the cornea.[5] For sake of simplicity, the classic term embryotoxon will be used in reference to these abnormalities of the trabecular zone and prominent anterior border-ring of Schwalbe.

Although the majority of authors attribute the first classic description of embryotoxon to Axenfeld, in 1920, the term can be found in medical dictionaries as early as 1894.[6] Von Hippel, in 1909, wrote the portion on embryotoxon in Axenfeld's textbook, discussing its etiology and associated congenital anomalies. Actually, descriptions of complexes that were undoubtedly embryotoxons were occasionally reported in the literature much earlier, but, for lack of recognition as entities, they were either misnamed or just included as incidental findings. An excellent example of this is the report of Landesberg in 1886.[7] In it he described two cases (one patient 17 days old and the other 10 days old) in which there were marginal opacities of the cornea similar to a gerontoxon, and, in addition, the 17-day-old infant had some pupillary distortion and knuckling at the ring border. Landesberg also pointed out that the 19-year-old mother of one of the patients had the same anomaly bilaterally.

The occurrence of additional congenital ocular anomalies associated with embryotoxon has been frequently described. The majority of these have been hypoplasia of the iris stroma, polycoria, corectopia, remnants of the pupillary membrane, megalocornea, and microphthalmos. It is not uncommon to find an associated glaucoma. Embryotoxon itself is believed to be not only congenital but familial, and it is thought that all these combined malformations are probably various grades of the same clinically complex entity.[8]

The following case report is believed to be the first described in which the associated congenital anomaly is vascular as well as on the surface of the globe.

A 33-year-old Caucasian woman was referred to the ophthalmology clinic of the U. S. Naval Hospital, Philadelphia, for a "cavernous hemangioma" of her right eye, noted on routine physical examination.

The patient gave a history of having had this lesion observed at birth and that the only manifestation of activity was the occasional episode of a so called "hemorrhage." These were characterized by painless blurring of vision occurring approximately once a month and lasting from one-half hour to weeks. She was told that these were due to bleeding in the anterior chamber. The patient felt that they had occurred more frequently in her childhood and that they were especially apt to occur just prior to the onset of her menses. In addition, postural changes, such as bending her

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The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

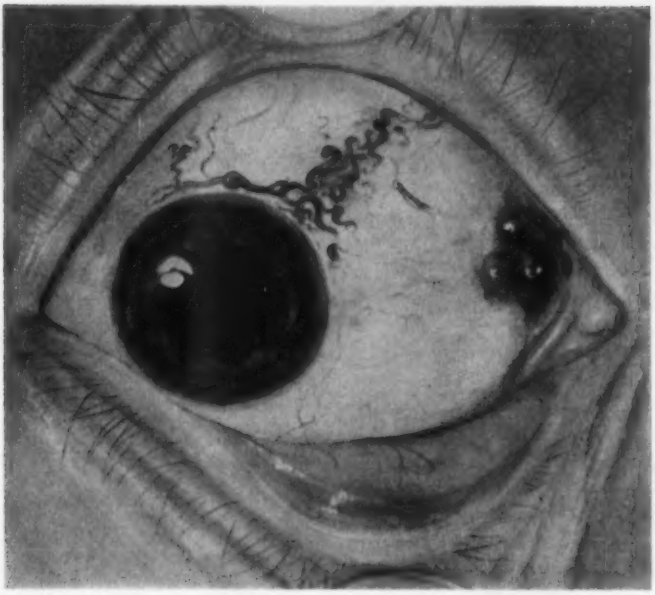
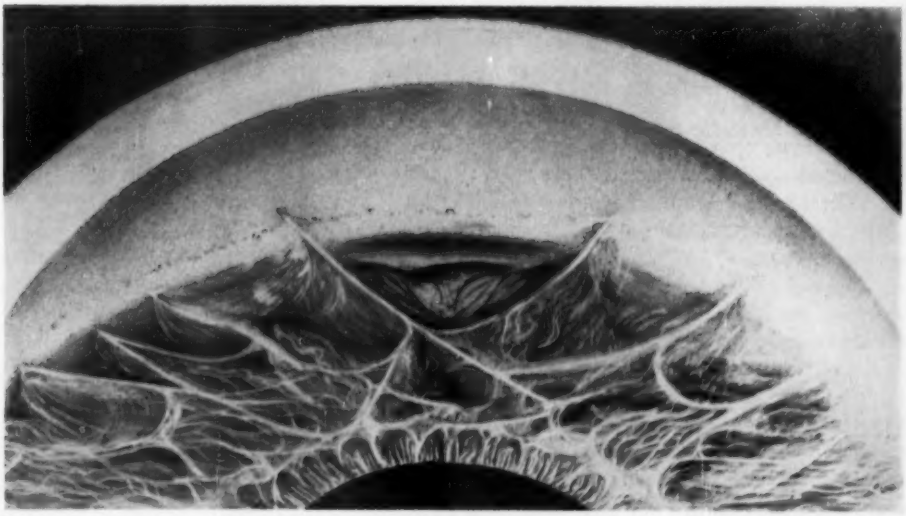


Fig. 1. — Hemangioma of the globe. Clinical appearance, showing venous-type vessels superior nasally and hemangiomatous tumor superior and deep to caruncle.

head either backward or forward, could at times initiate an episode. There was only one occurrence, at the age of 14, of a gross and painful hyphema. This subsequently cleared with no sequelae. The conjunctiva has never been involved in bleeding. The only time there has been any apparently rapid growth of the lesion was shortly after tion. Since then the lesion had remained an operation (left salpingo-oophrectomy) one month prior to the present examina- stationary.

Fig. 2.—Gonioscopic view of anterior chamber angle, showing bridging iris processes to and above Schwalbe's line, area of iris atrophy, and blood in Schlemm's canal.



The general physical examination, including skull x-rays and dermatological evaluation, was essentially normal. The visual acuity was 20/20 O. D. and 20/25 O. S., corrected to 20/20 with pinhole. Upon manual elevation of the eyelid, a large hemangiomatous tumor of the right globe was noted to be superior and deep to the caruncle. There was a large group of venous-type vessels that arose at the superior nasal aspect of the globe and extended down to the limbus but not onto the cornea (Fig. 1). The pupils, extraocular movements, peripheral and central fields, intraocular tension, and ophthalmoscopic examinations were all normal. Hertel exophthalmometer reading was 14×15/92. Gonioscopy of the right eye revealed several broad-based pigmented peripheral anterior goniosynechiae (bridging iris processes) attaching at and above Schwalbe's line. The remainder of the angle was open, and Schlemm's canal was noted to be filled with blood. A well-demarcated and depressed area of iris atrophy was noted peripherally at the 6 o'clock position. No abnormal blood vessels were noted (Fig. 2). The entire gonioscopic examination was typical of embryotoxon, and a clinical diagnosis of posterior embryotoxon with associated hemangioma of the globe was made. The diagnosis was confirmed by Dr. Harold G. Scheie, of the Hospital of the University of Pennsylvania.

Drawings by Marie Kern, with permission of Dr. Francis H. Adler, Hospital of the University of Pennsylvania.

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Ophthalmological Reviews

Developmental Anomalies of the Skull Affecting the Eye

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Introduction

Congenital anomalies of the eye have repeatedly been seen in cases of developmental anomalies of the skull. Such reports, however, comprise only certain aspects of this problem. Furthermore, they are scattered all over the various specialty journals and have appeared in many languages. The publication of a review on this subject was prompted by two main factors. First, the appearance of a monograph on the congenital anomalies of the ear occurring in developmental anomalies of the skull (Nager and DeReynier [1]) made a similar treaty on the anomalies of the eye more desirable. Secondly, I had the good fortune to see in our clinic, within a relatively short time, numerous patients affected with these anomalies. It is therefore hoped that this review, which approaches the subject from a broader aspect, may be of some use to the practicing ophthalmologist who has heretofore been confused by numerous case reports without integration.

Classification

The classification of these anomalies is difficult as long as the exact pathogenesis remains unknown. Numerous methods of classifying congenital anomalies of the skull exist, but many are confusing or inconsistent. I shall follow Nager and DeReynier and adapt their classification for the special problems that confront an ophthalmologist.

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The first section deals with anomalies of the cranium. These are the so-called craniostenoses, or dyskephalias. These anomalies may or may not be associated with malformations of the extremities.

The second section is concerned with anomalies involving the cranium and the facial skeleton. These are the craniofacial dysostoses of Crouzon, again, with or without malformations of the extremities.

In the third section anomalies affecting the facial skeleton alone are discussed. These comprise mainly the mandibulofacial dysostosis of Franceschetti.

Hypertelorism is the subject of the fourth section, and rare anomalies are presented in the fifth section.

At the end of each section an illustrative case or cases are described. These cases with the accompanying illustrations should only serve as representative examples. No attempt was made to report all the cases.

I. Craniostenoses

During the normal development of the bones of the skull areas of ossification appear in the cartilagenous and membranaceous ground substance. The bones of the base of the skull and the facial skeleton are originally cartilagenous, while the bones of the cranium are membranaceous. The areas of ossification grow larger and larger so that the ground substance slowly disappears, except for small stripes where it persists. These stripes are the sutures, which are really lines of junction where the bones are prevented from joining until the brain ceases

to grow. While the sutures of the base of the skull close early, the large sutures of the vault do not close before the 30th or 40th year of life. That means that they close long after the bones have stopped growing.[2,3]

A. Physiologic Variations.—If one suture line disappears earlier and the adjoining bones fuse sooner than normally, certain anomalies in the shape of the skull will develop. These are not pathologic unless they are pronounced and cause clinical symptoms. They are of great anthropologic interest.

Any such disturbance in the growth of the bones may cause a complete arrest of bone growth perpendicular to the suture line. If the skull can compensatorily grow in other directions, only anomalies in the form of the skull will result, without any other signs or symptoms. These skulls by themselves do not cause blindness, nor do they inhibit the mental development of the patient. High-vaulted heads have been noted in unusually gifted persons (e. g., Sir Walter Scott) or have been thought to be a mark of distinction (Chinese gods).

Two main types of variations are distinguished: the long head, with an early disappearance of the sagittal suture (dolichocephalus), and the short head, with an early closure of the coronary or the lambdoid suture (brachycephalus). The latter type is, for instance, frequent among the Southern Slavs in the Dinaric Alps.

It is interesting to note that artificially deformed skulls (e. g., the pre-Columbian Indians and the early inhabitants of Northern France) did not increase digital impressions nor were visual disturbances produced.

B. Pathologic Forms.[4]—In the true craniostenoses the bones fuse along one or more suture lines so early that a disproportion between skull and brain results. On x-rays the convolutional outlines will become prominent, and clinical signs and symptoms will be present.

1. Tower skull (turricephalus, oxycephaly). This is a hyperbrachycephalic skull and is probably the most common form of craniostenosis. It is an abnormally high skull caused by a premature fusion along transverse sutures and fissures, especially along the coronal suture. There will be a marked projection at the bregma, and the horizontal circumference of the skull may approach a circle.

2. In akrocephaly the anteroposterior diameter is also decreased. Here the anterior part of the sagittal suture is also involved, and this type of skull has been compared to a policeman's hat or a fireman's helmet.

3. A rarer form of craniostenosis is scaphocephaly. The length of these skulls is excessive, and their breadth is diminished. They have been compared to the shape of a canoe, and they are caused by premature fusion along the sagittal suture. Frontal and occipital areas bulge conspicuously, but clinical symptoms and signs are rare.

4. Craniostenosis may also be asymmetrical; the premature fusion may occur in one half of the skull only. An asymmetric skull (plagiocephaly) will result.

The patient's symptoms are first those of increased intracranial pressure, namely, headache, dizziness, and vomiting. Then symptoms of brain damage, such as mental retardation and epileptiform seizures, follow. If the optic nerves are involved, decreased vision will occur.

The deformed skull is the most prominent clinical sign. In mild forms it may only be appreciated on an x-ray film. The pathologic changes are not confined to the vault. The base of the skull may show aplasia and premature fusion. Some authors believe that these changes precede the anomalies of the skull. The anterior cranial fossa is shallow, and the greater wings of the sphenoid are thrust forward. The middle fossa is deep, and the posterior fossa is deep. The latter may be thrust downward and become funnel-shaped. The digital impressions will usually be conspicuous; the bones of the vault are thin, and the sella may be enlarged.

Anomalies of the nasal cavity and the palate occur frequently. Deviations of the nasal septum may also be present.

C. Ocular Involvements.—Damage to the eyes occurs commonly in craniostenosis, though this is not an inevitable complication.

1. Involvement of the Optic Nerve: Blindness is the most serious complication. It is produced by atrophy of the optic nerve. The cause for this atrophy has been discussed by many authors. The atrophy appears usually as a primary one, and for this reason atrophy secondary to papilledema seems to be excluded, or at least very rare. In a number of cases the optic atrophy seems to be due to a narrowing of the optic foramen. This was undoubtedly the case in one of my patients cited below, in whom atrophy occurred only on the side of the smaller foramen.

On the other hand, recent careful autopsy studies [5] showed that in some cases increased stretch on the optic nerve is the only cause for the atrophy. This stretching of the nerve is due to the increased flexion of the cerebral hemispheres. A knicking of the optic nerves by pressure of the internal carotid against the roof of the foramen has also been assumed to be a factor in producing optic atrophy.

2. Exophthalmos: As the greater wing of the sphenoid is thrust forward, the sagittal axis of the orbit is shortened. The roof of the orbit may also become inclined and approach a vertical plane. The volume of the orbit is in that way decreased, and the globes are pushed forward. The exophthalmos may be so severe as to jeopardize the eyes by exposure keratitis, ectropion of the lids, or true luxation of the globes.

3. Exotropia: Divergent strabismus is a frequent complication because of the divergent axes of the orbits.

4. Other Complications: These are rare. Nystagmus may occur because of amblyopia. Blue sclerotics, cataracts,[6] and medullated nerve fibers in the retina have been described in association with craniostenosis.

D. Treatment.—Most recent reports on craniostenosis deal with its early treatment. This is indicated not only in order to prevent mental retardation but also to protect the optic nerves. Blindness is one of the commonest and most tragic complications of craniostenosis, and an early operation is indicated to prevent it. Many modifications of these operations have been advised.[7-14] This is mainly a neurosurgical problem, and no evaluation of these operations will be attempted.

Representative Case.—A 9-year-old white boy was referred to the clinic because the left eye turned out. The left eye was known to have had poor vision for five to six years. He could not read very well and did not progress in school as fast as he should have (Fig. 1).

Fig. 1.—Profile of a 9-year-old boy with increased anteroposterior diameter of the skull (oxycephaly).

The eyes were normal except for the nerve heads. The left one was pale; the right one, nearly normal. There was an exotropia of 15 degrees with the right eye fixing. Vision in the right eye was 6/9; in the left eye 2/60.

X-ray of the skull revealed a markedly elongated anteroposterior diameter. The left optic canal was small (Figs. 2A and 2B).

Psychological studies showed a full-scale I. Q. of 52, which warrants the diagnosis of a mentally deficient child. The electroencephalogram had a slow, probably lateral, asymmetry in the occipital areas.

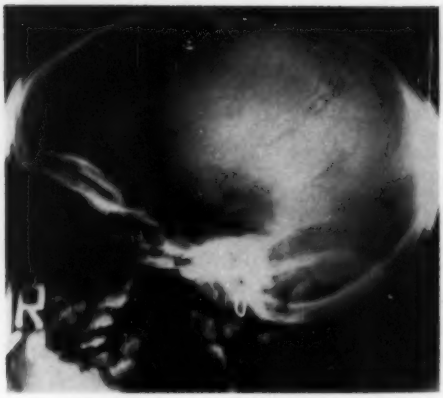

Fig. 2A.—Skull x-ray of the boy in Figure 1.

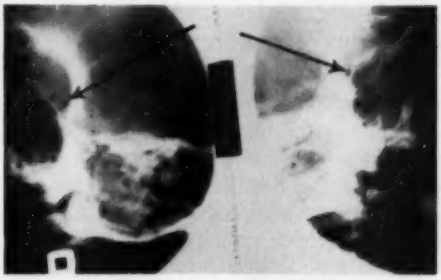

Fig. 2B.—The left optic foramen is markedly narrower than the right one.

This is an instance of oxycephaly in which the optic atrophy was caused by a smallness of the optic canal.

Akrocephalosyndactyly.—This combined malformation of the skull and the extremities was first thoroughly reviewed by Apert in 1906. The skull deformity is not characteristic; nor is it always of the same type in the reported cases. In addition, this syndrome may be associated with many and various other malformations. These malformations may affect not only the extremities (syndactyly, polydactyly, brachydactyly, arachnodactyly) but also the digestive tract and the skeletal system.

The ocular involvements are the same as those found in pure craniostenoses. Exophthalmos [15] and exotropia [16] have been reported. Mental deficiency is a frequent complication.[17]

Representative Case.—An 8-month-old baby was referred to the eye clinic because of a corneal ulcer in the left eye. There was bilateral exophthalmos, and the child was unable to close the lids on the left side. The skull showed a typical tower shape, and the four lateral digits were fused in all four extremities (Fig. 3).

Fig. 3.—Profile of an 8-month-old baby with tower skull and exophthalmos.

Fig. 4.—Skull x-ray of the baby in Figure 3.

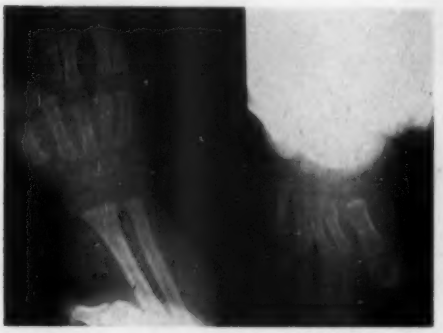

Fig. 5.—X-ray of the extremities of the baby in Figure 3. Osseous malformations and syndactylism are present.

X-ray of the skull revealed an oxycephalic configuration, with premature closure of the coronal sutures and underdevelopment of the sphenoid bone (Fig. 4). X-ray of the extremities showed numerous congenital anomalies, with bony syndactylism present only in the hands (Fig. 5).

Lid adhesions were done on the left side, and the corneal ulcer healed with a dense scar. Coronal craniectomy with orbital decompression was done on both sides.

II. Craniofacial Dysostosis

Crouzon,[18] in Paris, described (1912) for the first time the combination of cranial and facial anomalies called craniofacial dysostosis in two patients—mother and child. Since then, his name has been closely connected with this clinical entity.

A. Deformities of the Skull

The skull is usually brachycephalic, with the markings of a fully developed turricephalus. The thin skull bones bulge in the area of the anterior fontanella. The bone may even become dehiscent so that meninges and brain herniate.[19] This boss may extend laterally and occipitally. The occiput is flat. The head is usually flat in the temples are elongated upward.

B. Deformities of the Face

There is a typical atrophy of the upper jaw. The zygoma and the mandible are well developed. There is an inferior prognathism and malocclusion of the teeth.

The nose is broad and hooked. This sometimes gives the profile a resemblance to a parrot. Deviations of the nasal septum occur frequently.

The palate is high, and the implantation of the teeth in the upper jaw is irregular.

Anomalies of the ear have been carefully reviewed.[20] The ear lobe is often larger than normal. Atresia of the external duct is frequent. The middle ear shows anomalies in position and form.

The x-ray picture confirms the clinical impressions.[21] There are usually deep digital impressions. The coronary and the lambdoid sutures are synostotic. The entire basis of the cranium is depressed downward and backward. This shortens the anterior cranial fossa. Hypoplasia of the maxilla is conspicuous.

C. Ocular Anomalies

The changes of the eyes are secondary to the orbital anomalies. The pupillary distance is characteristically widened (hypertelorism), and the shortened orbits produce exophthalmos of varying degree. There is usually exotropia. The optic nerve may show the same variety of damages (papiledema, atrophy) as in other forms of craniostenosis.

D. Clinical Course

Crouzon considered the hereditary nature of this syndrome as an essential characteristic, and many of the reported cases do show a familial incidence.[22,23]

The anomaly is present at birth but becomes more conspicuous during the first year of life, when the head grows rapidly.

The increased intracranial pressure may be present at birth or may develop later. If it persists for a longer period of time, it will cause headaches, convulsions, mental deterioration, and optic atrophy.

E. Treatment

Decompression operations are indicated as in other forms of craniostenosis. These operations have been done with varying results.[24-27] It appears, however, that if they are performed at an early stage of increased intracranial pressure the results are promising.

Fig. 6.—A 4-year-old girl with aplasia of the maxilla.

F. Kephalodactyly

A combination of the craniofacial dysostosis with anomalies of the extremities was first described by Vogt.[28] Since then, a number of similar cases have been reported.[29]

This entity is therefore a combination of the symptoms of a craniofacial dysostosis with akrocephalosyndactyly. We find oxycephaly, hypoplasia of the maxilla, and syndactyly of the extremities.

Representative Cases

1. A 4-year-old girl was referred by Dr. J. A. Thorsen, of Dubuque, Iowa. The patient showed some exophthalmos and a deformity of the face caused by aplasia of the maxilla (Fig. 6). X-ray of the skull revealed conspicuous digital impressions and a maxilla markedly below average in size. Only one tooth, the left upper molar, had erupted (Figs. 7A and 7B).

2. An 8-year-old boy came to the hospital because of poor hearing, which was thought to be causing his poor progress in school. He was found to have congenital atresia of the ear canals with middle ear hearing loss.

The head was elongated, and the eyes were markedly prominent (Fig. 8). There was

Fig. 7A.—Skull x-ray of the girl in Figure 6 shows a small maxilla.

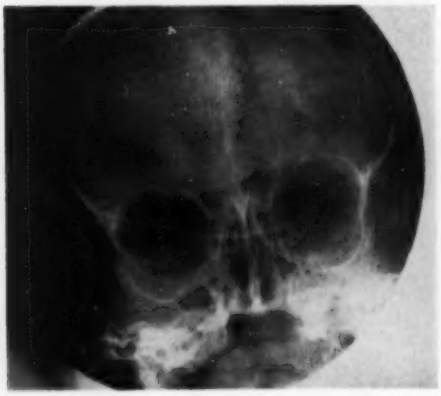

Fig. 7B.—Marked digital impressions in the same patient.

Fig. 8.—Two views of an 8-year-old boy with Crouzon's disease.

Fig. 9.—Skull x-rays of the boy in Figure 8.

marked exotropia of the left eye, and bilateral primary optic atrophy was found. Vision was 6/9 O. U., and the visual fields were markedly constricted.

X-ray pictures of the skull revealed craniostenosis, hypoplasia of the mandibles, and triangular-shaped optic foramina (Fig. 9).

Because of increased intracranial pressure, lowered intelligence quotient, and optic atrophy, a linear craniectomy was done. The visual acuity has since then remained 6/9 O. U.

III. Mandibulofacial Dysostosis

This form of cranial dysostosis has occasionally been observed in the past. The first descriptions probably came from Berry [30] and Collins,[31] in 1889 and 1900. Only a few additional observations were reported until 1943, when again English authors [32,33] could add three more patients to the small list of published cases.

It remained, however, for Franceschetti and his co-workers [34,35] to appreciate the importance of this clinical entity. They collected all the reported cases and integrated their own clinical material. This form of synostosis has therefore, quite justly, often been referred to as Franceschetti syndrome. Since Franceschetti's description, a number of cases have been reported,[36-39] some of them from this country.[40-43] Many of these case reports appeared in journals not easily available to American ophthalmologists, and this syndrome is therefore not as widely known in this country as it deserves to be.

A. Symptomatology

The main characteristics of this dysostosis are the following: 1. Hypoplasia of the facial bones, especially of the molar bones and the mandible. This gives the face of these patients the characteristic appearance which has been called "bird's face." The face is delicate and angular in contrast to the coarse features of the patients with a craniofacial dysostosis. The hypoplasia of the malar bones makes the inferior orbital margin indistinct, and this contributes to the malformations of the lower lid. The atrophy of the mandible causes a prognathism of the upper jaw and an open bite. The maxilla is normal except for an atrophy of the zygomatic processes.

2. Malformations of the lids. The palpebral fissure has a characteristic slope. The lids slant toward the temporal side. This has been called an anti-mongoloid appearance. In addition, there may be nicking and ectropion of the lower lid. These anomalies in the position of the lower lid are caused by the atrophy of the malar bones. There may be a coloboma in the outer portion of the lower lid.

3. Malformations of the ear.[44] There is symmetrical microtia and atresia of the external auditory canal. Anomalies of the inner ear may occur.

4. Anomalies in hair growth. There is frequently an extension of the hair line toward the cheek.

5. Other anomalies. Blind fistulas between mouth and ear, cleft palate, and other malformations have been described.

B. Clinical Variations

In addition to typical cases of this syndrome, the following variations may occur: 1. Incomplete form.[45-47] In these cases the anomalies are less striking and the ear is often normal. One of the first reported observations [31] probably belongs to this group.

2. Abortive form. Here only one of the signs is present, while other manifestations are visible in members of the same family. This proves convincingly the hereditary nature of this lesion. The first case report [30] belongs to this category.

Unilateral form.[45-47] A few unilateral cases have been reported with the complete form in the offspring. Because of the apparent rarity, we report here a typical unilateral case.

4. Atypical forms. These forms show only partial characteristics of the syndrome and may lead over to closely related conditions.

C. Pathogenesis

There can be no doubt that this syndrome is of a hereditary nature. It has been ob-

served through three generations [41] and seems to follow an irregular pattern of dominant transmission. There is a close relationship with otocephaly, as has been shown in animal experiments.[48] The gene must be fairly unstable, but this syndrome presents an independent genotypic entity.

The disturbances in development must occur early. It has been shown that they occur during the seventh week of embryonic life. The disturbance affects the structures deriving from the first and the dorsal part of the second branchial arches. Careful dissection of an infant affected with this condition revealed an anomaly of the stapedial arteries, which could be the primary defect.[49]

D. Associated Anomalies

Among the more important accompanying malformations may be the following: 1. Dermolipomas of the conjunctiva [37,43,44,50] have not infrequently been observed. 2. Multiple skeletal deformities,[45] especially of the vertebral column, have been described. 3. Anomalies of the extremities. The combination of this dysostosis with syndactyly and related anomalies is very interesting, especially when one compares the frequency with which other forms of craniostenosis or dysostosis may be associated with malformations of the extremities. The name akrofacial dysostosis [51] was applied to this association of mandibulofacial dysostosis and syndactyly. However, later reports [52] did not accept that term. Circumscribed alopecia may also be present.

E. Treatment

As far as the eyelids are concerned, the treatment has to be a plastic one. Grafting has been successfully performed.[33]

Representative Cases

1. A 12-year-old boy was born with a marked malformation of the auricles. Many operations were performed to improve their shape. There was also a severe anomaly of the middle ears, and the boy was deaf. A cleft palate was repaired early in life.

Fig. 10.—A 12-year-old boy with a typical Franceschetti syndrome.

Fig. 11.—A 5-year-old boy with a unilateral (left side) mandibulofacial dysostosis. Note the extra cartilages in front of the left ear.

X-ray of the skull revealed a hypoplasia of the mandible and malformation of the malar bones.

The palpebral fissures have an anti-mongoloid slant, and the lower lids are loose and not in contact with the bulbar conjunctiva. The globes and vision are normal (Fig. 10).

This is, therefore, a typical case of mandibulofacial dysostosis.

Fig. 12.—Dermolipoma in the lower fornix of the left eye of the boy in Figure 11.

2. A 5-year-old boy was born with a poorly developed left mandible. He had difficulty nursing because of the malformed jaw. The nasal septum was deviated, and extra cartilages were present in both external ears. The hard palate was unusually high (Fig. 11).

The vision was normal in both eyes. The lower lid of the left eye showed an anti-mongoloid slope. Two dermolipomas were found in the lower fornix of this eye (Fig. 12).

The x-ray picture of the skull revealed a small left mandible. The condyle and the coronoid process were not satisfactorily seen. There was no evidence of cranial synostosis. The right mandible was normal (Fig. 13). This is, then, a unilateral case of mandibulofacial dysostosis with conjuntival dermolipomas.

Fig. 13.—Skull x-ray of the boy in Figure 11, showing a small mandible.

Association with Severe Ocular Defects

In the classical cases of mandibulofacial dysostosis the eye itself remains intact. The changes around the eye are confined to the anomalies of the lids and occasionally to an epibulbar dermolipoma. Hallermann [54] and, later, Streiff [55] described cases of mandibular hypoplasia with severe ocular anomalies. Only three further reports have been published,[56-58] and so this combination seems to be rare. Yet I was able, within a short time, to observe two such patients in this clinic.

In these cases the eyes are microphthalmic and congenital cataracts are present. The patients are very intelligent but practically blind.

The nose is here also malformed, and that gives the face an appearance resembling a parakeet. In the classical form of Franceschetti's syndrome the patients have more the physiognomy of a fish or a duck.

Representative Cases

1. A white woman was first seen at the clinic in 1936. She was then 37 years old. She had had poor vision since birth. The diagnosis of bilateral microphthalmos was made, and vision in both eyes was found to be reduced to counting fingers at 1 meter. Both corneae showed zonular dystrophy, and membranous cataracts were present. The tension was normal to fingers in both eyes (Fig. 14).

The patient returned in August, 1954. She had been getting along well teaching in a school for the blind. For the last years her eyes had been painful and red.

The examination of the eyes at this time revealed, in addition, distichiasis of the left upper lid and a marked anti-mongoloid slope of the palpebral fissure. The left cornea was partly vascularized, and the right showed bullous keratopathy. The membranous cataracts had not changed. The intraocular pressure seemed elevated on palpation.

The most striking observation in this patient was the small mandible and the beak-like nose. This gave her profile the typical bird-like appearance. No eyebrows were present, and the lashes were scanty. X-ray of the skull showed a definite hypoplastic mandible with an infantile angle between the body and the mandibular rami.

Members of the ear-nose-throat department examined the patient and gave the following diagnosis: bilateral residual chronic otitis media with a mastoidectomy cavity

Fig. 14.—Microphthalmic eye in a patient with mandibulofacial dysostosis. Distichiasis of the upper lid and corneal vascularization are present.

on the left side and a postauricular scar, external nasal deformity, deviated nasal septum, microstomia, and bilateral mixed deafness.

The cilia on the left side rubbing on the cornea were epilated. The patient was given 2% pilocarpine q. i. d., and most of her symptoms disappeared.

2. A girl was first seen at the age of 4 months. At that time bilateral microphthalmos was found. Both lenses were cataractous. She was seen again at the age of one year. At that time the right eye was thought to be blind. The left fundus could be seen and appeared normal. The right lens was completely, the left only partially, cataractous.

The child was seen again at the age of 8. She had mentally developed very well. Because of her vision she attended a school for

Fig. 15. — Congenital defect of hair in an 8-year-old girl with mandibulofacial dysostosis.

Fig. 16.—Profile and front view of the girl in Figure 15.

the blind, where she made excellent progress. Her physical development was certainly retarded. She weighed only 34 lb. (15.3 kg.) and was 45 in. (112.5 cm.) tall. The expression of the face was that of a wizened old woman. There was a hair defect over the scalp on one side (Fig. 15). The mandibles were extremely short, with the tongue riding high in the mouth. The mouth was small, and there was crowding of the teeth. There was malocclusion of the jaws, with congenital absence of a number of teeth (Fig. 16).

Fig. 17.—The right microphthalmic eye of the girl in Figure 15. Note the absence of a catoptric image of the lens.

The otolaryngological examination revealed congential absence of the upper lateral and alar cartilages of the nose. The septum was widened and deviated, with bilateral nasal obstruction.

X-rays of the skull showed hypoplasia of the mandibles, with a general diminution of the size of the calvarium.

The ophthalmic examination revealed bilateral microphthalmos. The anterior chambers were deep. The right lens had completely disappeared (Fig. 17), and in the left eye only remnants of the lens were visible.

IV. Hypertelorism

This term was coined by Greig [59] to designate a wide separation of the orbits. He thought that it was caused by a developmental anomaly of the bones of the skull and that it represented an independent malformation. All the published cases have a similar facial expression, with laterally displaced eyes, flat nose, and shortened upper lip.

The most conspicuous ocular complication is exotropia, which may reach enormous degrees.[60] On the other hand, the external recti muscle may become paretic, and an esotropia results.[61] Optic atrophy,[60] microphthalmos, and microcornea [62] have been described.

Comparatively few cases of hypertelorism have been reported since the original paper in 1924. Twenty-one were collected in 1951.[63] It is noteworthy that most of these patients also suffered from other congenital anomalies. Most frequently observed were median clefts of the nose or the lips and deformities of the extremities.

Patients with craniostenosis and hypertelorism show that these two anomalies may be more closely related than was originally assumed.[64] Unusual is the occurrence of hypertelorism in a patient with mandibulofacial dysostosis as described in the extensive review by Gross.[65]

The ideas on the pathogenesis of this anomaly have changed a great deal. Greig originally assumed that an enlargement of the lesser wings of the sphenoid was the sole cause of hypertelorism. The lesser wings may ossify earlier, and the enlarged bones may press on the optic nerves. At the same time, the greater wings may be retarded in growth, rendering the orbits more circular and deeper.

This theory has now been generally abandoned. There exists a relatively wide

Fig. 18.—A 14-year-old boy with hypertelorism.

Fig. 19.—Skull x-ray of the boy in Figure 18.

intraorbital distance during human embryonic development. This, together with the frequent association of hypertelorism and facial clefts, is a convincing proof that hypertelorism represents an instance of arrested development.[62]

The frequent association of hypertelorism with malformations of various kinds makes it perhaps doubtful whether this is an independent anomaly at all. However, a few instances of isolated hereditary hypertelorism have been observed.[62,66]

Representative Cases

1. A 14-year-old boy was admitted because of a perforating injury of the left eye. He was mentally retarded. The skull appeared flat, and the interpupillary distance was conspicuously enlarged (Fig. 18).

X-ray of the skull showed a widening of the area between the orbits. The odontoid process was elevated above Chamberlain's line (Fig. 19).

This is an instance of hypertelorism associated with mental retardation. This association is frequent and indicates arrested development of the brain. A wide interorbital distance is apparently commoner among mentally retarded children than among normal children.[62]

2. A 50-year-old woman was known to have suffered from osteogenesis imperfecta since childhood. Other members of her family have the same affliction. She has had compression fractures of her spine and numerous fractures of her extremities.

The patient was of a definitely dwarfed structure, with scoliosis and partial collapse of the spine. She was completely deaf, and her slerotics had a bluish color. The interpupillary distance was obviously enlarged (Fig. 20).

Fig. 20.—A 50-year-old woman with osteogenesis imperfecta and hypertelorism.

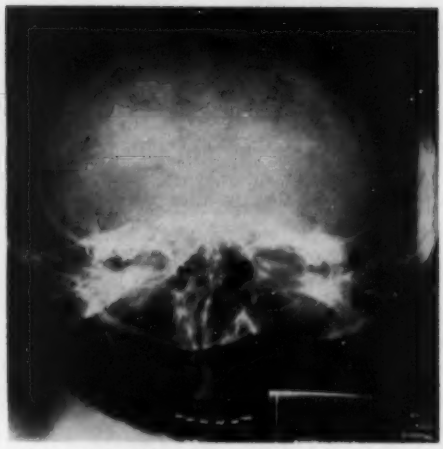

Fig. 21.—Skull x-ray of the patient in Figure 20, showing hypertelorism and platybasia.

X-rays of the skull showed the orbits to be spaced widely. Chamberlain's line was at the level of the third and fourth cervical vertebrae (Fig. 21).

This is an instance of hypertelorism associated with Van der Hoeve's syndrome. In addition, the patient had platybasia, and this condition is in my experience frequently associated with hypertelorism. One finds in platybasia a displacement of the occiput into the posterior fossa of the skull, with a narrowing of the foramen magnum. It is often found with other skeletal anomalies.

3. A 19-year-old boy was born with a short, thick neck and a deformed left ear. A flop ear was present on the left side instead of an auricle. The face was broad, and there was a marked increase in the intrapupillary distance.

X-ray of the skull showed increased distance between the medial walls of the orbits. In addition, the tip of the odontoid process extended above Chamberlain's line (Fig. 22).

Fig. 22.—Skull x-ray of a 19-year-old boy with hypertelorism and platybasia.

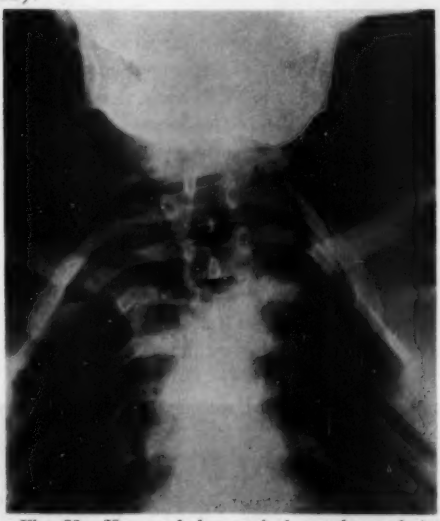

Fig. 23.—X-ray of the cervical vertebrae of the boy in Figure 22 reveals a Klippel-Feil anomaly.

X-ray of the neck revealed a fusion of several cervical vertebrae, with a rudimentary first rib on the right (Fig. 23).

This is, then, an instance of hypertelorism and platybasia associated with Klippel-Feil anomaly. Such an association has been observed not only with hypertelorism [67] but also with oxycephaly and corresponding ocular involvements.[68]

V. Rare Anomalies

A. Anomalies of Fusion. — Premature fusion of paired parts, for example the orbits, may occur.

Trigonocephaly is a premature synostosis of the frontal bones. A keel-like ridge appears on the forehead, and the orbits lie close together. The optic nerves may be damaged by pressure. There is a compensatory extension of the skull in length and height.

In arrhinencephaly the two median walls of the orbits are in contact. No true nose is present.

In cyclopia only one orbit is present and the fusional malformation may involve the globes.

B. Congenital Bony Defects.—1. Defects can be multiple as in lückenschädel. This may cause herniation of the meninges or of the brain.

2. Congenital defects in the upper orbital wall may cause pulsating exophthalmos.[69,70]

3. Hypoplasia of the orbital margin may be associated with vertical strabismus.[73]

C. Effects on the Eye from Distant Lesions

Developmental anomalies of the skull may indirectly affect the eyes. Platybasia has already been discussed in connection with hypertelorism. But this malformation may also decrease the volume of the posterior fossa and press on brain stem and cerebellum, causing vertical or horizontal nystagmus.[74]

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Annual Reviews

The Lens and the Vitreous

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As in former years, the literature on the lens and vitreous was voluminous in 1956. This review presents a survey of important developments in the field but does not attempt to report all the papers that have been published during the past year.

Surgery of the Lens

Preoperative Complications.—The treatment of patients with coexistent cataract and primary glaucoma has been discussed in several papers. Hughes [1] described an operation for the removal of the cataract at the same time that an anterior sclerectomy and iris inclusion operation was performed. Of 29 eyes in which this combined operation was performed, normal tension was restored without the use of miotics in all but 1 eye. Tamler and Maumenee [2] advocated the removal of the clear lens in the management of selected cases of acute iris-block glaucoma when the excessively high tension did not respond to medication or when the patient had had an acute attack for three or more days. However Leydhecker's review [3] showed that cataract extraction had little effect on the tension of 50 unselected glaucomatous eyes. In 31 eyes the tension was not permanently altered; in 11 eyes it dropped 6 mm. Hg(Schiøtz) or more, and in 8 eyes it rose 6 mm. Hg (Schiøtz) or more. In those cases with a tension of 45 mm. Hg (Schiøtz) before cataract extraction, Leydhecker recommended a primary antiglaucoma operation, but he stated that an Elliot trephine was contraindicated, since the subsequent cataract extraction was more apt to negate the drop in pressure obtained by the trephine operation.

There is still considerable difference of opinion on the most satisfactory method of removing a cataract in the presence of a filtering cicatrix following an antiglaucoma operation. Rizzuti [4] advocated removal of the cataract through an inferior limbal section when a filtering cicatrix is present above. Scheie,[5] on the other hand, favored an incision in clear cornea in front of the filtering cicatrix. He thought that best results were obtained by making the incision vertically perpendicular to the corneal surface rather than with a bevel.

Removal of the clear lens was also advocated for the treatment of high myopia by Valerio,[6] who stated that in only 3 eyes out of 70 was vision lost following this operation for myopia of over 16 D. In the remaining eyes visual improvement varying from 2/10 to 5/10 occurred. Castroviejo [7] pointed out the need for removal of the lens, whether cataractous or not, in total penetrating keratoplasty.

Instruments.—The introduction of the new Ethicon eye sutures, with needles of extreme sharpness, described by Hughes,[8] has proved of marked advantage for cataract surgery. Dekking [9] has presented a simplified and improved operating microscope for use in eye surgery, based on the design of the Zeiss otoscope. Controls regulated by the feet and knee vary the position of the instrument, which must be used with an especially designed clamp to immobilize the patient's head.

A knife which resembles a cystotome was described by Atkinson [10] for making a safe cataract section. When the shaft of the

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knife is held firmly against the globe, a nonperforating incision is made; when the handle is elevated, raising the heel, a perforating incision is cut. Sato [11] described a thin corneal knife to be used for discission of congenital cataract or capsular remains without causing collapse of the anterior chamber during the manipulations. Kulvin [12] suggested the use of a laboratory wire basket to provide an air-way tunnel; it is clamped next to the patient's chin under the surgical drapes. This simple device should prove useful in preventing the feeling of suffocation experienced by many patients during operations under local anesthesia. Ordinary small round paper clips were found to be helpful in controlling stiff absorbable surgical (gut) sutures by Yudkin,[13] and a forceps for placing corneoscleral sutures has been described by Ambrose.[14]

Anesthesia.—During the past year there has been extensive consideration of the most efficient and satisfactory anesthetics and relaxants to use for ocular surgery. In addition to numerous individual papers, these topics were especially considered at the annual meetings of the Ophthalmological Society of the United Kingdom and of the American Academy of Ophthalmology and Otolaryngology. From a review of these papers it seems that the use of general anesthesia is losing its vogue.

Atkinson,[15] in surveying the techniques used by 454 ophthalmologists, found that 93% used local anesthesia routinely and that 95% did not use curare. For preoperative preparation pentobarbital (Nembutal) sodium or secobarbital (Seconal) sodium combined with meperidine hydrochloride (Demerol) was preferred. Antiemetic drugs such as chlorpromazine hydrochloride (Thorazine), dimenhydrinate (Dramamine), or promethazine (Phenergan) hydrochloride were often used. Procaine or lidocaine (Xylocaïne) combined with epinephrine and hyaluronidase were used most frequently for akinesia and retrobulbar injection. The van Lint procedure was favored 2:1 over the O'Brien method. After the retrobulbar injection, Atkinson recommends firm pressure on the globe through closed eye lids to aid in establishing the anesthetic and akinetic effect. Swan [16] has presented an excellent review of the newer drugs and techniques for local anesthesia. He points out the advantages of benoxinate (Dorsacaine), dyclonine (Dyclone), and Ophthaine (a preparation containing 2-diethylamino-ethyl-3-amino-4-propoxy-benzoate hydrochloride, chlorobutanol, glycerin, and benzalkonium chloride) for topical anesthesia. He gives a good summary of the ocular effects produced by injections in different anatomic locations. Injections made near the apex of the orbit with a needle 2 in. (5 cm.) long produce the greatest motor paralysis but have the largest risk of retrobulbar hemorrhage. A midorbital injection with a needle 1½ in. (3.75 cm.) long is recommended for the routine injection. Placing anesthestic solution under the posterior portion of Tenon's capsule by an injection under one of the rectus muscles has been found to be useful in detachment surgery. Injections made under the anterior portions of Tenon's capsule produce greater anesthesia of the anterior segment than those made subconjunctivally.

Efforts are being made to lengthen the time local anesthesia is effective. Scheie [17] has presented a technique for inserting a fine polyethylene tube into the muscle cone with a retrobulbar needle which is withdrawn over the tube, leaving the tube in the muscle cone. Repeated injections of local anesthetic solution may then be made to prolong the anesthesia or to relieve postoperative pain. Prolonged akinesia for several days has been attempted by the injection of procaine and butyl aminobenzoate in a nontoxic organic solvent. Paez Allende [18] reported satisfactory results with use of this method, but Dastoor [19] found it unsatisfactory because of the variability in the length of akinesia produced and the

intense local irritation caused by the material injected.

The routine use of general anesthesia for cataract surgery is still recommended by Sandiford[20] and Cridland,[21] who described in detail the method they employed. Conflicting reports appeared on the use of curare. Argañaraz[22] stressed its importance, as did Ramsay.[23] Healy[24] pointed out the usefulness of tubocurarine in cataract operations in an early report, but in a later one[25] he favored operation under local anesthesia. Bramford[26] stressed the dangers of respiratory embarrassment with the administration of curare and stated that he had completely abandoned its use after a trial in 88 cases. Nutt[27] reported that he also no longer used curare. In its place he obtained good results by the use of chlorpromazine administered intravenously by the technique of Wilson[28]: Secobarbital, 1½ grains (0.1 gm.), was prescribed the evening before operation. One hour before surgery, 0.1 gm. of secobarbital and 50 to 100 mg. of meperidine hydrochloride were administered intramuscularly. Fifteen minutes before surgery 1 ml. per minute of a 20 ml. solution containing 50 mg. chlorpromazine hydrochloride and 100 mg. meperidine was given. The dose usually required was from 20 to 45 mg. of chlorpromazine hydrochloride and from 40 to 90 mg. of meperidine hydrochloride. Oxygen was supplied through an artificial airway. Burn[29] stated that he had used chlorpromazine and meperidine and had found them unsatisfactory. He concluded that, if local anesthesia was used, it was better to operate under barbiturate sedation and leave the patient's self-control relatively unimpaired. Sadove[30] also strongly cautioned against the use of chlorpromazine because of its powerful potentiating effect on sedatives and hypnotics. He stressed the dangers of general anesthesia and recommended that thiopental (Pentothal)-nitrous oxide anesthesia never be used unless an adequate retrobulbar block had been secured first. He advocated increased use of the sedative action of the antihistaminics, such as promethazine, chlorpheniramine (Chlor-Trimeton), and diphenhydramine (Benadryl).

As an attempt to avoid the dangers of general anesthesia, Birge et al.[31] described an anesthetic technique intermediate between full general anesthesia with endotracheal intubation and local anesthesia. They employed thiopental hypnosis, but found that the chief risks were laryngospasm, coughing, and sneezing.

As found by Atkinson,[15] most surgeons prefer proper psychologic and medical preoperative preparation combined with local anesthesia as a routine procedure, reserving general anesthesia for the psychotic, hard of hearing, or markedly apprehensive patient, as pointed out by Burch[32] and Clark.[33]

Simultaneous Surgery.—A few years ago Duthie advocated simultaneous operations on the two eyes in cases of bilateral cataracts. In a recent paper[34] he presented the results obtained by such surgery in 70 cases and recommended its use in selected cases.

Technique.—(*a*) Incision: Sobhy[35] advocates placing the limbal incision in the region where the zonule is torn, when operating to remove partially luxated lenses. When the lens is completely luxated, he often finds it necessary to transfix the lens before extracting it.

(*b*) Sutures: The usefulness of a corneoscleral suture at 12 o'clock to act as a control in opening and closing the corneal flap is discussed by Kingston.[36] The use of plasma and thrombin to seal the conjunctival flap is recommended by Barraquer-Moner,[37] who also describes two methods of placing nonabsorbable surgical (silk) sutures subconjunctivally. Curtin and Boyes[38] review the difficulties of removing sclerocorneal sutures and outline the technique which they have found effective.

(*c*) Method of Extraction: Haik and Jimenez[39] reported their experiments on 12 enucleated eyes, from which they concluded that pressure should be placed on the pos-

terior lip of the limbal wound with a lens loop at the 10, 12, and 2 o'clock positions. At the same time, counter-pressure should be applied below with a muscle hook. These maneuvers aided in breaking the zonules, after which the lens was delivered by tumbling.

Apparently the erisophake is becoming more popular. Pearlman [40] in a statistical study of 1337 senile cataract extractions found that use of the Bell erisophake as compared with the lens forceps produced a lower rate of capsule rupture and less lens residue when the capsule was inadvertently ruptured. The preservation of a round pupil did not increase the rate of capsule rupture or vitreous loss. The rate of vitreous loss did not seem to be influenced by the addition of hyaluronidase to the retrobulbar injection. Villaseca [41] has made an extensive and interesting study of the physical dimensions of the various forms of erisophake cups. He shows how the adhesive force produced by the various cups depends upon their dimensions and points out the features in the design of the cups that influence the force of adhesion generated. He describes an ingenious method for producing a variable, measurable, and controlled vacuum based on the simple displacement of mercury between two bottles. Silvan [42] describes a foot pedal with a steel wire attached to a rubber sleeve by means of which pressure can be placed on the erisophake bulb, thus freeing the fingers for the delicate work of placing the erisophake on the lens.

Intraocular Lenticular Substitutes.—Riddell [43] points out the dangers of the Ridley operation and stresses the need for extreme care in the selection of patients for this operation. He states that the operation should be limited to patients with monocular cataract who have good vision in the better eye and therefore have a reasonable chance for binocular vision following the operation. He feels that the operation is contraindicated in myopia or in persons with diabetes or hypertension and that it should not be used in traumatic cataract if the lens is partially dislocated or the zonule damaged. Smith [44] has reported the histopathologic findings in nine eyes enucleated after the implantation of a Ridley acrylic lenticulus. In all cases, fibrosis in the vicinity of the lenticulus was the most prominent feature seen. Gormez [45] described his experience in two cases with Ridley lenses. In one the lenticulus became displaced into the anterior chamber, and in the other a secondary glaucoma occurred.

Interest in the operation utilizing Strampelli's plastic lens in the anterior chamber is increasing, but there are still numerous difficulties, as reported by Barraquer-Moner.[46] In his first case, a pupillary block glaucoma developed, which was controlled only by cyclodiathermy. To prevent this, the author recommended peripheral iridotomy.

Postoperative Complications.—That early postoperative ambulation is not to be feared seems to have been proved dramatically by the strange experience reported by Holland.[47] At one of his operating camps in India during 1955, a sudden torrent forced 100 cataract patients, all operated upon at various times during the preceding six days, to run 100 yards, sit up all night in a crowded hut, walk to lorries the next morning, drive over rough roads, and walk to a schoolhouse used as a temporary shelter. Two days later the patients again walked to the lorries and were driven back over bumpy roads to their original camp site. Inspection of the eyes showed no complications, except in one old woman who had hit her eye against the corner of a table during the confusion of the exodus.

Georgariou [48] studied the postoperative complications in 7209 cases of cataract extraction. He recommends phlebotomy and diuretics for those patients with blood pressure over 200 mm. Hg and coagulants for those with increased bleeding time or low prothrombin values. He advises the injection of air into the anterior chamber following the extraction. Postoperative

glaucoma was treated by cyclodialysis and cyclodiathermy, and simple diathermy was successful in 75% of the aphakic detachments. Payne, Simonton, and Cury [49] studied 333 eyes enucleated because of complications following cataract extraction. Uveitis was by far the largest cause for enucleation, occurring in 205 eyes, and in three-fourths of these the uveitis was complicated by secondary glaucoma. Epithelial invasions were the second most common cause for enucleation, accounting for 60 eyes. Most of the eyes removed were from patients who had had extracapsular operations.

In the Bowman lecture, Dunnington [50,51] pointed out the complications that result from imperfect healing of the cataract section, especially hyphema, iris prolapse, flat anterior chamber, and epithelial invasion. He reviewed the normal healing of the wound and discussed the need for adequate sutures and the influence of cortisone and thrombin on the healing process. He stated that most of the serious complications following cataract surgery can be attributed to imperfect wound healing. In a separate paper [52] he elaborated on postoperative hypotony, which occurs either as a short-lived immediate complication or as a chronic late complication. These cases of hypotony, Dunnington stated, must be treated by discovery and closure of the leak in the incision.

Acetazoleamide (Diamox) has been found useful in the reestablishment of flat anterior chambers following cataract extraction when no leaking of the incision can be found. Thorpe [53] has found that a total dosage of 1000 mg. of acetazoleamide orally per day is effective in most cases. If the anterior chamber does not reform within a few hours, he recommends that the administration of acetazoleamide be continued for four to five days. Burch [32] has also found acetazoleamide useful in the management of flat anterior chambers. Lassiter [54] reccomends posterior sclerotomy and air injection for those cases with late persistent collapse of the anterior chamber after cataract extraction. In a selected series, secondary glaucoma was found in 19% of 36 untreated eyes with flat anterior chambers, while glaucoma did not occur in 15 eyes on which posterior sclerotomy and air injection had been performed. Chandler [55] agreed with Lassiter and stated that he operates if the anterior chamber has been flat for five days, while Dvorak-Theobald [56] reported that she did not allow the anterior chamber to remain flat for more than two days. On the other hand, Guyton [57] pointed out the dangers of this operative procedure and cited the low incidence of glaucoma attributed to flat anterior chambers in the two series of Bellows, Lieberman, and Abrahamson [58] and Hughes and Owens.[59] Castroviejo [60] stated that in his experience rushing to restore an anterior chamber that has remained flat for a few days or even a few weeks has done more damage than good. Jaffe and Light [61] reported a case in which reestablishing the anterior chamber was successful only after mechanical separation of the iris from the cornea was done with a cyclodialysis spatula introduced into the angle through a suprachoroidal approach followed by the injection of air through the suprachoroidal cleft. Voisin and Juge [62] found that galvanocautery puncture with a retinal detachment point was an effective way to open the sclera in the region of the choroidal detachment.

Macular edema may follow the hypotony that sometimes occurs after cataract extraction. Dellaporta [63] reported four cases after intracapsular cataract extraction, and Nicholls [64] described nine cases. In five of Nicholls' cases the edema occurred some time after operation, and in four of them there was an associated prolapse of the vitreous forward into the anterior chamber. Swelling of the cornea following cataract extraction has been reported by Giardini and Cambiaggi,[65] who measured the corneal thickness in 37 eyes following cataract extraction and found that the cor-

nea became thicker, especially in its upper portions.

Various forms of treatment of epithelial invasion of the anterior chamber have been reported during the past year. Georgariou [48] found that simple cysts could be treated easily by puncture or excision, while epithelial sheets in the anterior chamber could not be successfully treated even with β-rays or cortisone. The ease of treatment of postoperative cyst was also reported by Esposito,[66] who used aspiration and the injection of 50% glucose solution. Kennedy [67] reported the successful treatment of four iris cysts and one epithelial cyst by the use of electrolysis, and Maumenee and Shannon [68] reported successful treatment of epithelial cysts by excision with a large iridectomy and curettage of the corneal endothelium if necessary. Wheeler,[69] however, reported an unfortunate outcome when radon was used after excision of an epithelial cyst.

A review of 55 cases of postoperative glaucoma found in 2200 cases of cataract extraction has been reported by Jayle, Ourgaud, and Gérin-Bonnet.[70] Most of the cases were treated with cyclodialysis. The results in general were poor, and the authors stress the importance of preventive measures.

Abnormalities in the appearance of the face of the vitreous on the 10th to 12th day after uncomplicated operation were studied by Holland [71] in 508 cases of cataract extraction. In 81% the hyaloid membrane was found to be intact. In the remaining cases, varying amounts of vitreous had imperceptibly escaped into the anterior chamber at operation. The author found little difference in the postoperative appearance of the face of the vitreous when the forceps method of cataract extraction had been used, in comparison with the Smith technique.

Attempts to further decrease the incidence of postoperative infection have been reported by Locatcher-Khorazo and Gutierrez.[72] These authors recommend the routine use of local antibiotics for several days before cataract extraction and again during the postoperative period. They found the chief pathogen in their cases to be Micrococcus (Staphylococcus) aureus, which was usually present in the eyelids. They believe that, during recent years, the incidence of a carrier state for this organism has greatly increased, as has the resistance of the organism to antibiotics. Pearlman [73] studied the effect of a prophylactic subconjunctival injection of a solution containing 100,000 units of penicillin combined with 10,000γ of streptomycin on the incidence of purulent endophthalmitis following cataract extraction. No cases of endophthalmitis occurred in 3226 operations when this prophylactic injection was used, while an incidence of 0.24% occurred in 1202 cases when penicillin alone was injected and an incidence of 0.5% developed in 1773 cases when no prophylactic injection was given. The subconjunctival injection of the combination of penicillin and streptomycin was followed by some increase in postoperative pain and external inflammation.

McGavic [74] has reviewed the literature on the toxic and anaphylactic properties of the lens and has reported a case with bilateral phacoanaphylaxis in which both eyes were examined histologically. Leigh [75] describes cases with a phacoanaphylactic type of uveitis in the unoperated on eye following extracapsular cataract extraction.

The pathologic findings in four cases of expulsive hemorrhage following cataract extraction have been described by Manschot,[76] who found that the hemorrhage was due to the rupture of a necrotic posterior ciliary artery resulting from hampered intramural circulation.

Coles and Linn [77] have reported on behavior disturbances in patients undergoing cataract extraction.

Congenital Cataracts.—Gregg [78,79] has reviewed the diagnosis and treatment for congenital cataracts which appear following maternal infection with rubella. He advises early operation but stresses the surgical dif-

ficulties and the poor prognosis in these cases.

Chandler [80] has discussed his preferences in operating on patients with congenital cataracts. Unless the opacity is so dense as to preclude useful vision, operation is deferred to the age of 5 to 7 years. A complete iridectomy above and an iridotomy below are employed to obtain an adequate pupillary opening and prevent glaucoma from pupillary block. A linear extraction is preferred. The most serious complication at operation is vitreous loss, the danger of which can be lessened by firm pressure on the globe for five minutes before the operation. He states that retinal detachment is a frequent postoperative complication.

The Jackson Memorial Lecture, delivered by Cordes,[81] included an excellent study of the histopathologic findings in 56 enucleated eyes following extraction of congenital cataract. From his study Cordes concludes that linear extraction is the safest operation for congenital cataract and multiple needlings the least desirable one. He recommends a complete iridectomy if the pupil does not dilate fully preoperatively.

Clinical Observations of the Lens

Congenital Malformations.—A case of the syndrome which has been aptly named "bird face and congenital cataract" by Hallerman has been described by Leffertstra.[82] He pointed out the three salient characteristics of the syndrome: (1) abnormal shape of the skull, (2) congenital bilateral cataracts, and (3) abnormally sparse growth of hair on the scalp.

Lisch [83] considers abnormalities of the tunica vasculosa lentis as the pathogenetic factor in lenticonus posterior and in microphakia.

Rosenthal and Kloepfer [84] have described five cases of the Marchesani syndrome (spherophakia-brachymorphia) occurring in two families. They conclude that the disease is transmitted as an autosomal recessive with partial development of the syndrome in heterozygous carriers.

An unusual case of bilateral symmetrical and almost congruent indentations of the lens and cornea has been described by Livant.[85] Mitter [86] has reported an interesting case of dislocated lenses. The patient could voluntarily place his bilaterally dislocated lenses into the anterior chambers by lowering his head and permit them to fall back in the vitreous by placing his head backward. This patient had been followed for three years without signs of ocular irritation.

Cataracts Associated with Endocrine Disorders.—The characteristics of the cataracts found in hypoparathyroidism have been reviewed by Schlossman,[87] who emphasized that this condition should be suspected in all patients under the age of 40 who develop cataracts. In a study of 1300 diabetics, Dollfus [88] found that under the age of 45 years 70.5% of the patients were free of ocular complications. In his series there were 35 patients who had cataracts of the diabetic type, and all of them were under 50 years of age. Galactosemic cataracts were described by Turnbull [89] in two sisters, one 7 weeks old and the other 2½ years of age.

Cataracts Associated with Skin Disorders

A case of rapidly developing cataracts in a man aged 39, in association with a hypersensitivity reaction to the systemic administration of penicillin, has been described by Daniel.[90] Gilkes [91] has reported three cases of cataracts in association with neurodermatitis. He emphasizes the difficulties of obtaining sterile cultures before operation and the frequency of iritis and retinal detachment following operation in these cases.

Senile Exfoliation of the Lens Capsule.—An excellent monograph has been published by Sunde [92] on senile exfoliation of the anterior lens capsule. He describes the clinical and histological appearance of exfoliation of the lens capsule, stressing the difference between the peripheral band and the central disc. From his studies, Sunde agrees with Malling and Busacca that the

granular material forming the peripheral band is a deposit and that there are no changes in the lens capsule itself. He states that the glaucoma often present is not caused by the so called "exfoliation," but that the two conditions share a common cause.

Miscellaneous Observations.—Appelmans, Michiels, and Missotten [93] have described a patient with the pulseless syndrome, who showed the characteristic triad of lack of radial pulse, cataract, and vascular changes in the fundus.

A case of cataract due to dinitrophenol has been described by Hermann,[94] who points out the necessity of keeping this etiologic factor in mind when dealing with cataracts in young people.

Cataracts induced by heat from an iron rolling mill have been studied by Coates and Keatinge.[95] They found lens changes more frequently in workers exposed to the furnaces than in a control group of men from a mental institution. In the development of this type of cataract, capsular striations appear early, followed by posterior capsular changes, then exfoliation of the anterior capsule, and finally development of posterior cortical changes.

Ryan [96] described the appearance of bilateral cataracts between the 6th and 10th weeks in a premature infant suffering from gastroenteritis and anemia. The cataracts matured rapidly in less than four weeks.

Neame [97] reports the use of a dark eye shade attached to the top of the spectacle frame to improve the vision in patients with incipient cataracts.

An unusual case is described by Samuels,[98] of a 2½-year-old child who developed an abscess in the posterior portion of the lens after his eye had been pecked with the beak of a cock.

Corin [99] has reported a case of apparently complete spontaneous absorption of a cataractous lens and its capsule. However, in the absence of pathologic studies there is a possibility that the lens fell into an area of the vitreous hidden to ophthalmoscopic view.

Parker [100] has reported an additional case of spear cataract.

Laboratory Investigation of the Lens

In a new textbook on the comparative anatomy of the eye, Prince [101] has devoted one chapter to the lens, which deals with the variations in the structure of the lens that occur in aquatic, semiaquatic, and land vertebrates and in animals with nocturnal and diurnal habits.

A histologic study of the epithelial cells of the lens is reported by Niessen.[102] He concludes that morphologically similar cells form the epithelium of the lens. This is in contrast to the findings of others, who have described various forms of cells in the lens epithelium.

Pirie and van Heyningen [103] have published a book of interest to both the clinical ophthalmologist and the general physiologist. In three chapters devoted to the lens, they give an excellent summary of the chemical composition of the lens and a review of the knowledge of its enzymatic metabolism. This book should be read by all. It not only summarizes the present state of information on the lens but indicates the large gaps in our knowledge and the vast domain unexplored.

Lens Proteins.—Newer methods of investigation are gradually increasing the knowledge of the proteins that compose the lens. Dische, Borenfreund, and Zelmenis [104] studied the changes in the total protein, soluble protein, and insoluble protein in the lens of rats during aging. They determined the cysteine and cystine content of the protein fractions and the susceptibility of the protein fraction to oxidations. They found that the aging of the lens is associated with continuous oxidation of the cysteine to cystine and with continuous precipitation of insoluble protein. This process is analogous to keratinization in the epidermis. From their studies they conclude that during aging the

cystine of the insoluble protein (albuminoid) is derived, at least partly, from the cysteine of the soluble protein. However, the formation of the insoluble protein is not due to a direct precipitation after oxidation of the soluble protein but to more complex synthetic processes. In these processes, certain amino acids, such as cysteine, may not be available in sufficient quantities from the circulation, and so cysteine derived from the breakdown of soluble lens proteins may be utilized to continue the steady formation of insoluble protein. A "growth protein" may be an intermediate in the transformation of soluble protein into insoluble protein.

The antigenic mosaic of the lens protein has been studied by François, Rabaey, Wieme, and Kaminski,[105] using immunochemical analysis. Previous electrophoretic studies have shown the presence of three protein fractions in the bovine lens. Immunochemistry has demonstrated at least eight antigens. It was shown that electrophoretic Fraction III has two antigens, A and A′; electrophoretic Fraction II has two antigens, B and B′, and electrophoretic Fraction I has only one antigen, C. Three accessory antigens ac_1, ac_2, and ac_3 were found, which did not correspond to any demonstrated electrophoretic fraction. Electrophoretic fraction I (α-crystallin) is the only antigen in the lens that possesses organ specificity, and it is likewise the only antigen that has been present in all the mammalian lenses studied thus far. François, Rabaey, and Denucé[106] have studied the amino acid content of α-crystallin, using the method of paper chromatography. They found that 17 different amino acids are present in pure α-crystallin, whether it is obtained from the cortex or from the nucleus of the lens.

Metabolism of the Normal Lens.—An extensive and lucid summary of phosphate metabolism is given by Muller et al.[107] in an excellent report that should be read in its entirety. They found that most of the phosphate passes through the epithelium to enter the lens by metabolic activity and not by simple diffusion. They consider that glycogenolysis is probably not important in lens metabolism, as glycogen was not found in the lens. High-energy phosphate compounds (adenosinetriphosphate and phosphocreatine) are generated in the lens by the enzymatic processes of glycolysis, the hexosemonophosphate shunt, and the citric acid cycle and by the oxidative path of cytochrome and cytochrome oxidase. In addition, numerous accessory redox systems are active in the lens, such as glutathione, cysteine-cystine, and ascorbic acid. Their studies were made by following the uptake and distribution of radioactive phosphorus in normal metabolism, in the aging of the lens, when metabolism is inhibited experimentally, and during the development of various types of cataract.

Terner, Leopold, and Eisenberg[108] studied the radioactive phosphorus uptake in 4 eyes with senile cataract and in 10 eyes with complicated cataract. A positive test was found in only one case, with a cataract secondary to granulomatous uveitis and glaucoma.

Green and Solomon[109] have studied the effect of aging on metabolism, using cell-free extracts of the lenses of rabbits. They found that the cell-free extract from the whole lens of 3-year-old rabbits has a capacity to produce lactic acid which is 50% to 75% greater than that obtained from the whole lens of 4-week-old rabbits.

Attempts have been made to study the metabolic activity in the various separate anatomic parts of the lens. In the fibrous portion of the lens capsule, Dische[110] has demonstrated the presence of two metabolic systems, namely, glycolysis and an enzyme system which was able to break down ribose-5-phosphate. In addition, the lens capsule has been found to contain glutathione, which is rapidly oxidized in the presence of air. Wortman and Becker[111] describe a microtechnique which has enabled them to study the activity of enzyme systems in the various portions of the adult rabbit lens, such

as the anterior or posterior capsule of the nucleus and cortex.

Other investigators have studied the metabolism of the living lens with its capsule intact. Such investigations, although complicated by the problem of tissue culture and the entrance of metabolites into the lens through the lens capsule, probably give a truer picture of conditions as they exist in vivo. Leinfelder and Schwartz,[112] using a tissue culture technique, have measured metabolic activity by the ability of the lens to remain clear and to maintain its dehydration. Their results indicate that the sources of energy available to maintain clarity and dehydration are glycolysis and respiration. Interference with either anerobic glycolysis or aerobic respiration causes cloudiness of the lens and hydration, as measured by the increase in weight of the lens. These authors feel that the measure of oxygen consumption by the older technique of Warburg is a measure of nonenzymatic auto-oxidation of reduced substances present in the lens, chiefly glutathione and ascorbic acid, and therefore not a true index of the enzymatic metabolism. Harris and his co-workers[113,114] have used another method for studying the metabolism of the intact whole lens. They found that the maintenance of a high potassium and low sodium concentration by the lens depends upon active metabolism. When the intact lens is placed in the cold, potassium is lost and sodium gained. However, upon reincubation at room temperature, the former high potassium and low sodium concentrations are reestablished. This is named the "reversible cation shift" and is a useful tool in studying the factors that support metabolism. They found that compounds which can be metabolized via the citric acid cycle or the hexose-monophosphate shunt do not cause the recovery of potassium concentration as well as does glucose itself. This is thought to be due largely to the slow diffusion of the metabolites of the citric acid cycle into the lens in contradistinction to the action of glucose, which seems to enter the lens by active metabolic processes.[107,110]

Another method of studying the metabolism of the lens has been revealed by the discovery of Brindley[115] that the intact living lens has a resting potential, electrically negative to the extent of about 70 mv., as compared with its surroundings. This potential is abolished when potassium replaces sodium in the solution surrounding the lens. From his studies Brindley concludes that the potential is probably due to a difference in ionic content on two sides of a membrane which is 30 times as permeable to potassium as to sodium. In regard to cataract formation, measurements of changes in this electrical potential may give an indication of whether the first change is in the metabolism of the lens or in the permeability of its capsule.

Davson[116] has reported that the thiourea uptake by the in situ lens of rabbits is faster in younger animals than in older ones. Chatterjee and Ghosh[117] have found that the ratio of ascorbic acid in the aqueous to that in the serum is approximately the same in patients with aphakia, early cataract, and complete cataract, showing that the metabolism of the lens is not responsible for the ascorbic acid in the aqueous.

Metabolism of the Cataractous Lens.—Patterson[118,119] points out that the formation of experimental diabetic cataracts can be prevented, even in the presence of hyperglycemia, by feeding a special fructose high-fat diet that supplies substances capable of providing energy by being metabolized without insulin. These findings indicate that hyperglycemia, per se, is not the cause of diabetic cataract. Patterson concludes that diabetic cataract is caused by the lack of insulin, which prevents the utilization of glucose and thereby reduces the total amount of energy available to the lens. He stated that the cataract of galactosemia is produced by a similar loss of energy available to the lens through interference with normal phosphorylation by galactose. Dische, Boren-

freund, and Zelmenis [120] have found that the lenses of rats on a galactose diet have 100% inhibition of the synthesis of soluble lens proteins, although the inhibition of the synthesis of insoluble lens protein is no more than 20%.

A lack of vitamin E has been shown to cause cataracts in turkey embryos obtained from E-deficient hens. Ferguson, Rigdon, and Couch [121] have found that such vitamin E cataracts show extensive liquefaction of the lens protein and degeneration and proliferation of the lens epithelium, with some of the epithelial cells extending continuously along the posterior surface of the lens. In addition to the lens changes, occasional areas of focal degeneration are found in the cornea.

Radiation Cataracts.—Cataract can be produced in rabbits by either microwaves or ultrasonic waves. Williams et al.[122] have found that cataracts are produced by a single dose of microwave diathermy about four times the amount used in standard clinical treatments. Moore et al.[123] have produced transient cataracts by ultrasonic energy which raises the temperature of the vitreous up to 68 C. Bachem [124] has studied the biologic effects of the ultraviolet spectrum. He found that rays of 2970 A. units are most effective in producing cataracts; those of shorter wave length do not produce lens injury, and those of longer wave length produce cataract by cumulative effect.

Sinsky [125] and Kandori and Masuda [126] have given two excellent long-term studies on the victims of the Hiroshima and Nagasaki atomic bombings. Their finding are similar. Tiny polychromatic subcapsular plaques were found in about one-quarter of those exposed. The incidence of the cataracts could be correlated with age, degree of epilation, shielding, and distance from ground zero. Vision was 20/20 or better in over half of those with cataracts, but it is expected that the cataracts will develop further in coming years.

Kandori [127] made a study of the cataractogenic dose of x-ray for 3-month-old rabbits. He found that a single large dose is more harmful than fractionated doses. For instance, with a single exposure, the cataractogenic level is 900 r. When the individual dose is reduced to 150 r given twice weekly, the cataractogenic level rises to more than 1500 r. If the individual dose is reduced to 15 r given daily, no cataract forms after 185 days of exposure, or a total dose of 2775 r. He found that the minimum cataractogenic dose is lower than the epilation dose but that the lens has the same ability to recover from x-ray irradiation as other tissues. Leinfelder and his co-workers [128,129] studied another aspect of the dose of x-ray required to produce cataracts. They exposed one, two, or three quadrants of rabbit lenses to x-radiation as high as 12,000 r, which is many times the amount needed to produce cataract. They found that if only one or two quadrants are exposed only partial cataract develops in the exposed quadrant and the shielded quadrant remains clear. In some manner the shielded half seems to prevent the progression to a complete radiation cataract in spite of the high dose of x-ray. On the other hand, if three quadrants of the lens are exposed, a complete cataract occasionally develops. Becker, Constant, Cibis, and Ter-Pogossian [130] have found that irradiation of the rabbit eye with doses of 100 to 1300 r results in an inflammatory exudation into the anterior chamber, a partial suppression of aqueous formation, and an inhibition of lens epithelial mitosis. Pretreatment with steroids does not block the inhibition of mitosis but blocks the exudation and partially blocks the suppression of aqueous formation. These observations support the thesis of x-radiation having a direct effect on the lens epithelium.

Sallman [131] has presented a good review on the effects of ionizing radiation on the lens. He states that the lens is more sensitive to fast neutrons, alpha particles, and deuterons than to x-rays and that the peripheral portion of the lens is more sensitive than the central area. He reports a great

variation in susceptibility among different animal species and describes the pathologic findings, as does Kandori.[132] With small doses, the pathologic studies showed migration of epithelial cells to the posterior suture and pseudoepithelial proliferation under the posterior capsule. In the posterior cortex many bladder cells were found, which further degenerated into fat globules. In the equatorial bow the nuclei decreased in number and appeared in the posterior cortex, so that the angle of the bow was lost. With large doses of radiation the nuclei of the bow disappeared completely and bladder cells or vacuolization could be seen at the equator of the lens. François and Beheyt[133] have showed that the lens is protected from ordinarily cataractogenic doses of x-rays if the sulfhydryl compound cysteamine is given intravenously to rabbits before exposure. Nordmann and Mandel[134] have found a rapid change in enzymatic activity following exposure of rabbit lenses to a single dose of x-rays of 1400 r. There is a rapid increase of adenosinetriphosphatase activity and a decrease of hexokinase activity. From this they conclude that a deficiency in sugar metabolism occurs promptly after exposure to x-rays.

Solomon, Light, and De Beer[135] have reported that a new radiomimetic chemical, busulfan (1, 4-bis[methylsulfonyloxy]butane), useful in the treatment of chronic myeloid leukemia, produces an irreversible cataract in rats when administered in doses 10 times those used therapeutically in human beings. The cataract, which could not be prevented by various nutritional and chemical adjuncts, resembled the opacities caused by irradiation.

The Vitreous

From slit lamp studies, Faure and Goldmann[136] have found the vitreous to have a definite structural composition, consisting of concentric sacs around Cloquet's canal. The walls of the sacs coalesce in the peripheral region of the vitreous near the ciliary body. With age and myopia, cavities and fibrillary degeneration appear in the interior of the sacs. With the passage of time the cavities increase, leading to a detachment of the hyaloid membrane by fluid leaking through the posterior vitreous face. Varga[137] has described the vitreous body as a multicomponent fine gel built from long, highly asymmetric macromolecules, in which the solute is in low concentration in respect to the solvent. The gel is elastic, and is very near its limit of swelling ability. The viscosity of the vitreous is dependent upon its two major chemical components, hyaluronic acid and residual protein. Boruchoff and Woodin[138] have found that removal of either of these components by filtration reduces the viscosity of the vitreous. They also have found that hyaluronidase produces liquefaction of the vitreous gel. Howe[139] has found that the vitreous gel can be liquefied by electromagnetic radiation.

Analysis of the vitreous has led Balazs[140] to the conclusion that it consists of (1) a collagen type of protein, (2) a noncollagen type of protein, and (3) hyaluronic acid. The vitreous gel in adult mammals is visualized as a structural network of collagen filaments reinforced by the hydrated hyaluronic acid molecules. The collagen content is highest in the ciliary region. Neither collagen nor hyaluronic acid alone can maintain the gel state. An enzymatic analysis of the protein, made by Suran and McEwen,[141] showed three fractions. The first was hydrolyzable by trypsin and contained hydroxyproline and hexosamine. The second fraction, suggestive of collagen, was resistant to trypsin but was hydrolyzed by collagenase. The third fraction was resistant to both trypsin and collagenase and did not contain proline or hydroxyproline. Brunish[142] has studied the stability of the protein fibers obtained from beef vitreous by determining the temperature at which shrinkage occurs at various pH levels. By comparison with the behavior of whole rabbit vitreous, he concludes that the isolated

fibers are not derived artefacts. He found that hyaluronic acid bound less water when depolymerized and suggests that the hyaluronic acid-hyaluronidase balance may regulate the turgidity of the vitreous.

The physiology of the vitreous is less well known than is its chemical and physical structure.[143] The enzyme carbonic anhydrase has been found in low concentrations in the vitreous by Gloster.[144] It occurs principally in the peripheral area, and its presence is probably due to diffusion from surrounding tissues. The same conclusion of metabolic inactivity is drawn from the studies of Green, Mann, and Sawyer,[145] who found that the concentration of bicarbonate ion in the vitreous adjacent to the lens is higher than that in the posterior portion of the eye. They attribute this to diffusion into the vitreous from the lens. When the bicarbonate ion concentration in the blood plasma is artificially increased by the continuous intravenous infusion of isotonic sodium bicarbonate, the concentration rises in the aqueous but not in the vitreous humor adjacent to the posterior chamber. From their experiments they conclude that no significant net exchange occurs between the bicarbonate ion in the aqueous of the posterior chamber and that in the vitreous.

Paufique and Moreau[146] have reported their clinical experience with vitreous transplants using lyophilized vitreous. The lyophilized vitreous is a white powder, which regains the viscosity and transparency of fresh vitreous after rehydration. In aphakia, the powder was injected through the pupil via a limbal keratotomy. In other cases it was injected through a sclerotomy. The authors report its use in 15 patients, most of whom had vitreous hemorrhages, and they found that the anatomic results were satisfactory, although the functional results were disappointing because of the underlying ocular diseases. Moreau[147] has reported one case in which a vitreous transplant was made after removal of a copper foreign body. He suggests that an immediate graft of lyophilized vitreous be employed in cases such as this if there has been an extensive loss of vitreous.

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CORRECTION

In the article "Heparin in Senile Macular Degeneration: Preliminary Report," by Dr. Sol Rome, in the February issue (p. 190) the date in the legends for Figures 1A and 1B should be June, 1951, instead of 1956.

News and Comment

ANNOUNCEMENTS

National Council to Combat Blindness.—The National Council to Combat Blindness, Inc., 30 Central Park South, New York 19, in accordance with its program concerned with the financing of research in ophthalmology and related sciences, announces that application for its 1957/1958 Fight for Sight Grant-in-Aid and Fellowship awards will be considered at the Eighth Annual Meeting of the organization's Scientific Advisory Committee, to be held in the spring of 1957. This Committee has been enlarged to nineteen, and its members are the following:

Chairman: Charles A. Perera, M.D., Associate Professor, Department of Ophthalmology, Columbia University

James H. Allen, M.D., Chief, Department of Ophthalmology, Tulane University
Bernard Becker, M.D., Professor and Head, Department of Ophthalmology, Washington University School of Medicine

Alson E. Braley, M.D., Director, Department of Ophthalmology, University of Iowa
Frederick Crescitelli, Ph.D., Department of Zoology, University of California
Arthur G. DeVoe, M.D., Chief, Department of Ophthalmology, New York University-Bellevue Medical Center

Dan M. Gordon, M.D., Assistant Professor, Department of Ophthalmology, New York Hospital-Cornell Medical Center

Charles Haig, Ph.D., Associate Professor, Department of Physiology and Pharmacology, New York Medical College

Michael J. Hogan, M.D., Professor, Department of Ophthalmology, University of California
Peter C. Kronfeld, M.D., Professor, Department of Ophthalmology, University of Illinois
Irving H. Leopold, M.D., Director of Research, Wills Eye Hospital, Philadelphia
A. E. Maumenee, M.D., Director, Department of Ophthalmology, Johns Hopkins University
Karl Meyer, M.D., Associate Professor, Department of Biochemistry, Columbia University
Stuart Mudd, M.D., Professor, Department of Microbiology, University of Pennsylvania
Lorrin A. Riggs, Ph.D., Professor, Department of Psychology, Brown University
T. C. Ruch, Ph.D., Chairman, Department of Physiology and Biophysics, University of Washington

Samuel L. Saltzman, M.D., Assistant Professor, Department of Ophthalmology, New York Medical College

Kenneth C. Swan, M.D., Director, Department of Ophthalmology, University of Oregon
Phillips Thygeson, M.D., Professor, Department of Ophthalmology, University of California

The closing date for receipt of completed applications for Grant-in-Aid and Fellowship awards is April 15, 1957.

Applications for Summer Student Fellowships will be reviewed in advance of the meeting, and such applications should be filed with the office of the organization no later than April 1, 1957.

All applicants for fellowships are required to make their own arrangements for suitable research facilities with accredited institutions.

Appropriate forms may be obtained by addressing Secretary, National Council to Combat Blindness, Inc., 30 Central Park South, New York 19.

The 1956/1957 Fight for Sight awards of the National Council to Combat Blindness, Inc., approved by the members of its Scientific Advisory Committee are as follows:

Grants-in-Aid

Investigator	Institution	Amount	Project Title
Endre A. Balacz, M.D.	Retina Foundation, 30 Chambers St., Boston	$2500.00	Studies on the cortical layers of the vitreous body, with special regard to its mucopolysaccharides content
Goodwin M. Breinin, M.D.	Department of Ophthalmology, New York University-Bellevue Med. Center, 550 First Ave., N. Y. C.	4000.00	Electromyography of the extraocular muscles, including stimulation studies and evaluation of drug effects on the action currents
Robert Brunish, Ph.D.	School of Medicine, University of California at Los Angeles	842.00	Hyaluronic acid and hyaluronidase in ocular tissue
Max Chamlin, M.D.	Albert Einstein College of Medicine, Yeshiva University, Eastchester Rd. & Morris Park Ave., N. Y. C. (61)	1200.00	Development of equipment and a method for the determination of a previously unused isopter in the intermediate field of vision and the determination of this isopter in normal subjects
Max Chamlin, M.D.	Same	1200.00	Size of the normal blind spot: physiological variations and variations due to techniques used in measurement
Paul Anton Cibis, M.D.	Dept. of Ophthalmology, School of Medicine, Washington University, St. Louis 10	4000.00	Histopathology of the eye with oblique illumination
Bruce Edmond Cohan, M.D.	Dept. of Ophthalmology, Univ. of Chicago Clinics, Chicago	450.00	Outflow of aqueous humor: an experimental study using radioopaque materials
Robert S. Coles, M.D.	Post-Graduate Medical School, N. Y. University-Bellevue Med. Center, 550 First Ave., N. Y. C.	1026.00	The evaluation of antistreptolysin titers in patients with uveitis as part of a comprehensive program for the study of this disease in the Dept. of Opthalmology at N. Y. U.-Bellevue Medical Center
Levon K. Garron, M.D.	School of Medicine, University of California, San Francisco	4400.00	Special histopathologic study of endogenous uveitis
Harry Green, Ph.D.	Wills Eye Hospital, Philadelphia (30)	5700.00	Intraocular pressure and the bicarbonate ion concentration in animal eyes

Investigator	Institution	Amount	Project Title
Dan M. Gordon, M.D.	New York Hospital-Cornell Med. Center, 525 E. 68th St., N. Y. C.	3150.00	Application of visual aids in patients with subnormal vision
John E. Harris, Ph.D., M.D.	Univ. of Oregon Medical School, 3181 S. W. Sam Jackson Park R., Portland, Ore.	4500.00	Excretion of melanocyte-stimulating hormone in patients with certain ocular diseases
Jerry Hart Jacobson, M.D.	New York Eye & Ear Infirmary, 218 Second Ave., N. Y. C.	4500.00	Electroretinography in retinal disease: electrophysiology of the eye
P. J. Leinfelder, M.D.	Dept. of Ophthalmology, State University of Iowa, University Hospitals, Iowa City	1485.00	The effect of change of pH in the aqueous on metabolism of the lens and cornea
I. C. Michaelson, M.D.	Dept. of Ophthalmology, Hadassah Univ. Hospital, Jerusalem, Israel	1235.00	I. Factors affecting new vessel growth in the cornea II. Changes in hyaluronic acid content of vitreous in physiological and pathological conditions
Yukihiko Mitsui, M.D.	Dept. of Ophthalmology, Kumamoto University Medical School, Honjo-machi, Kumamotoshi, Japan	600.00.	Study of trachoma virus by cultivation and electron microscopy
Burton M. Pogell, Ph.D.	Wilmer Ophthalmological Institute, Johns Hopkins University Medical School, Baltimore (5)	4800.00	Metabolism and turnover of mucopolysaccharides in cornea and lens
Magin Puig Solanes, M.D.	General Hospital, Mexico, D. F.	2400.00	Comparative anatomical and physiological study of the structures related to the maintenance of intraocular pressures in Mexican Indians, "mestizos," and white people
Jun Tsutsui, M.D.	Dept. of Ophthalmology, Okayama Univ. Medical School, Okayama-shi, Japan	1000.00	Clinical and virological studies on trachoma, especially immunity, spontaneous cure, and tumor-like nature of the infected tissues
Jerome J. Wolken, Ph.D.	Biophysics Research Lab., University of Pittsburgh, Eye and Ear Hospital, Pittsburgh	2600.00	Photoreceptor structures

Investigator	Institution	Amount	Project Title
William C. Frayer, M.D. Francis Heed Adler, M.D.	Hospital of the University of Pennsylvania, Philadelphia	3000.00	A study of the factors involved in the proliferation of the retinal pigment epithelium in disease
Louise L. Sloan, Ph.D.	Wilmer Institute, Johns Hopkins Hospital, Baltimore	500.00	Evaluation of reading aids for patients with subnormal vision
Edgar Auerbach, M.D.	Hadassah University Hospital, Jerusalem, Israel	5000.00	Light and Color Perception

Fellow & Institution	Direct Supervisor	Amount	Project Title
Albert B. Chatzinoff, M.D., Mt. Sinai Hospital, Dept. of Ophthalmology, Fifth Ave. & 100th St., New York	Frederick Theodore, M.D.	$1500.00	Chronic deficiency of 11-cis vitamin A as the possible etiology of retinitis pigmentosa
Anthony Donn, M.D., Institute of Ophthalmology, London (W. C. 1)	David Maurice, M.D.	4000.00	The active transport of ions across the corneal epithelium and endothelium
Tibor George Farkas, Department of Anatomy, Western Reserve Univ., Cleveland	Normand L. Hoerr, M.D.	3000.00	Role of insulin in the metabolism of the lens
Harding Ernest Bishop, Department of Anatomy, University of Chicago	Prof. Isidore Gersh	2400.00	Retinal ultrastructure and possible functional changes in retinal ultrastructure
John A. Pratt-Johnson, M.D., Wilmer Eye Institute, Baltimore	A. E. Maumenee, M.D.	3600.00	Corneal transplantation with particular reference to elimination of the delayed sensitivity reaction as a result of homotransplantation; also, the metabolism and turnover of mucopolysaccharides in cornea and lens, as well as other chemical and allergic reactions which take place in the recipient's eye

Student Research Fellowships

Fellow & Institution	Direct Supervisor	Amount	Project Title
Irwin Willard Abrahams, N. Y. U.-Post-Graduate Medical School, Department of Ophthalmology, New York	Antonio Fernando, M.D.	$500.00	A study of radioactive labelled antigens in experimental uveitis

Fellow & Institution	Direct Supervisor	Amount	Project Title
Boris Andrst, N. Y. U.-Bellevue Med. School, Dept. of Ophthalmology, New York	George N. Wise, M.D.	600.00	Pathogenosis of retinal microaneurysms
Leslie Allan Bard, Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore	Burton Pogell, M.D.	600.00	Possible intermediates in the corneal synthesis of mucopolysaccharides
Arthur Berken, Washington University School of Medicine, Department of Ophthalmology, St. Louis	Bernard Becker, M.D.	600.00	The study of retinal and renal capillaries
Robert Emmet Moran Jr., Wilmer Institute, Johns Hopkins Hospital, Baltimore	A. E. Maumenee, M.D.	600.00	Corneal transplantation with particular reference to elimination of the delayed sensitivity reaction as a result of homotransplantation
Richard B. Oglesby, Washington University School of Medicine, Department of Ophthalmology, St. Louis	Bernard Becker, M.D.	600.00	The effect of trauma on aqueous flow
Melvin Lynne Rubin, University of California Medical School Francis I. Proctor Foundation, San Francisco	Michael J. Hogan, M.D.	600.00	The antitoxoplasmic activity of three chemotherapeutic agents
Ernest H. Shin, Biophysics Research Lab., Eye and Ear Hospital, University Medical Center, Pittsburgh	J. J. Wolken, Ph.D.	450.00	Kinetic studies related to bleaching of visual and photosynthetic pigments
Lawrence Isom, University of California School of Medicine, Francis I. Proctor Foundation, San Francisco	William K. McEwen, Ph.D.	400.00	Production and measurements of experimental glaucoma in monkeys

Ophthalmology Course at Walter Reed Army Medical Center.—Ophthalmologists from across the country have been invited to attend the Third Biennial Postgraduate Course in Ophthalmology at Walter Reed Army Medical Center, Washington, D. C., March 18-20. From 3000 to 4000 leaders in the field are expected to participate in the program, which is being held in conjunction with the Sectional Meeting of the American College of Surgeons.

According to Col. William L. Spaulding, Chief of Walter Reed's Eye Clinic, "those who had originally planned to stay for just one day, after seeing the program have expressed the desire to spend the entire three days in study." Topics to be covered in the postgraduate course range from corneal transplantation to glaucoma to cataract surgery. Papers reflecting the latest concepts in diagnosis, treatment, and care of patients will be delivered.

Members of the Walter Reed staff who will lecture during the sessions are Col. Francis W. Pruitt, Chief of the Department of Medicine; Drs. Frank B. Walsh and G. Victor Simpson, Walter Reed consultants; Lt. Col. George J. Hayes, Chief of the Neurosurgery Service; and Drs. James A. Stokes and John R. Weimer, senior residents in ophthalmology. Speakers will also include Dr. Lorenz E. Zimmerman and Lt. Col. Raymond A. Skeehan Jr., of the Ophthalmic Pathology Section of the Armed Forces Institute of Pathology.

Other physicians on the program will be Trygve Gundersen, Byron Smith, Ramon Castroviejo, Charles Iliff, Merrill J. Reeh, Marshall M. Parks, Arthur J. Jampolsky, Ludwig von Sallman, Francis Heed Adler, Harold G. Scheie, Paul A. Chandler, Joseph S. Haas, Kenneth E. Hudson, A. Edward Maumenee, Derrick Vail, Harvey E. Thorpe, Joseph Wadsworth, Irving Leopold, John S. McGavic, Charles L. Schepens, James O'Rourke, and Benjamin Rones.

Orthoptics for Technicians.—The Basic Course in Orthoptics for Technicians, sponsored by the American Orthoptic Council, will be held in the Department of Ophthalmology, University Hospitals, Iowa City, from June 19 through Aug. 10, 1957. As usual, there will be didactic lectures and practical demonstrations, given by an outstanding faculty. Further information and application blanks may be obtained by writing to Hermann M. Burian, M.D., Department of Ophthalmology, University Hospitals, Iowa City.

Central Illinois Society of Ophthalmology and Otolaryngology.—The Central Illinois Society of Ophthalmology and Otolaryngology will meet at the Urbana Lincoln Hotel, Urbana, Ill., on April 5, 6, and 7, 1957. Speakers will be Mr. Jack Copeland, Chicago; Dr. Henry P. Wagener, Rochester, Minn.; Dr. Kenneth Craft, Indianapolis.

Association for Research in Ophthalmology.—The Meeting of the Midwestern Section of the Association for Research in Ophthalmology will be held in the Department of Ophthalmology, College of Medicine, State University of Iowa, Iowa City, on Saturday, March 30, and Sunday, March 31, 1957.

Ophthalmology Residency Fellowships.—Six additional Fellowships for Residents in Ophthalmology, to begin July 1, 1957, have been announced by the Guild of Prescription Opticians of America, Inc., through its President, Galen B. Kilburn, of Atlanta. Applications for these fellowships must be received by May 15, 1957.

Each fellowship is for a total of $1800, payable in monthly stipends over the period of a three-year residency. The grants are limited to residences at approved institutions where full three-year residences are offered. Each grant is made for the entire three years, to begin the first year. Application forms and covering information are available by writing to Fellowships, Guild of Prescription Opticians of America, Inc., 110 E. 23d St., New York 10.

The six new fellowships being granted represent one for each of the six areas into which the United States and Canada have been divided upon the basis of a nearly-equal number of eligible residences in each area. The selection of the resident fellow is made by a committee of ophthalmologists in each area.

The Guild provides all fellowship funds as well as the program's cost of administration. Together with the six guild fellowships awarded last year, this year's new fellowships will bring the total to twelve, and next year the program will reach the permanent level of eighteen fellowships.

Course in Slit-Lamp Biomicroscopy and Ocular Surgery.—The Committee on Postgraduate Education of the Montefiore Hospital announces an advanced course in Slit-Lamp Biomicroscopy of the Living Eye combined with additional courses in Ocular Gonioscopy, Indirect Ophthalmoscopy, Surgery of Intraocular Foreign Bodies, Surgery of Cataract, and Retinal Detachment Surgery, to be given by the Montefiore Department of Ophthalmology under the direction of Dr. Harvey E. Thorpe and associates. These courses will be given at the Montefiore Hospital, Pittsburgh, for five days, May 6 to 10, 1957, inclusive, from 8:00 a.m. to 4:00 p.m.

The fee for the course is $80.00. A deposit of $25.00 is required for registration.

For further information write to A. McNabb, Secretary of Postgraduate Ophthalmic Courses, 206 Iroquois Building, Pittsburgh 13.

Guest speakers will be Dr. Robert J. Masters, Indianapolis, and Mr. Lee Allen, Iowa City.

New York University Post-Graduate Medical School Course.—Ophthalmic Plastic Surgery will be offered as a part-time course April 1 through 5, from 2:00 to 5:00 p.m., under the direction of Dr. Sidney A. Fox. Special emphasis will be laid on the fundamental procedures of lid surgery, as well as the classical operations for the correction of ptosis, ectropion, entropion, skin lesions, etc. Instruction will be by means of lectures and observation of surgical procedures in the operating room. Tuition is $85.

For further information, write to the Dean, Post-Graduate Medical School, 550 First Ave., New York 16.

GENERAL NEWS

Grants for Eye Research.—The National Society for the Prevention of Blindness has announced recent grants totaling $26,500 for ten eye research projects.

According to Dr. Franklin M. Foote, Executive Director, the awards are as follows:

Dr. Arnall Patz, Baltimore, $5000, Retrolental Fibroplasia; New York Eye and Ear Infirmary, $2000, Electrophysiology of the Eye; University of Nebraska Medical School, Omaha, $4000, Adrenocorticoid Function in Relation to Diabetic Retinitis; Wills Eye Hospital, Philadelphia, $3000, Choroidal Circulation; New York University-Bellevue Post Graduate Medical School, $2000, Pancreatic Dornase in Inflammatory Ocular Exudates; Washington University School of Medicine, St. Louis, $2500, Photo-Coagulation of the Retina; Albert Einstein College of Medicine, New York, $1000, Fields of Vision Studies; Medical College of Georgia, Augusta, $2000, Bacteriology of Uveitis; University of Chicago, Department of Pharmacology, $2500, Synthesis of Carbon-14 and Sulfur-35 Radioactively Labelled Diamox; Beth Israel Hospital and Massachusetts Eye and Ear Infirmary, Boston, $1500, Development of Effective Apparatus to Test Vision in Early Infancy by Means of Optico-Kinetic Response.

The National Society's grant for continuing studies in retrolental fibroplasia is part of a $15,000 grant established in 1953 by the E. Matilda Ziegler Foundation.

The nation's leading nonprofit sight conservation agency, the Prevention of Blindness Society carries on a year-round program of research, service, and education. The organization is supported by voluntary contributions to its headquarters at 1790 Broadway, New York 19.

Books

The Visual Fields. By David O. Harrington, M.D. Price, $16.00. Pp. 327, with 234 illustrations and 9 color plates. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

Several textbooks have appeared within the last few years to replace the gap left by Traquair's death, whose book for many years served students and trained ophthalmologists as an authoritative source on visual fields. None, however, have quite measured up, in either quality or ground covered, to Traquair's text, in the opinion of this reviewer, until the appearance of this book. It even far outdoes Traquair's in many respects, particularly the illustrations, which are truly magnificent and won the author the first prize in the scientific exhibit of the American Academy of Ophthalmology and Otolaryngology for 1956.

In general the material follows Traquair's plan, Part I consisting of the examination of the visual field and dealing with techniques and anatomy of the visual pathways and Part II containing the interpretation of defects in the visual fields on the basis of an anatomical arrangement. Some objection might be raised to the simplification which the author has probably purposely produced in the presentation of the individual fields from patients, as all of us know from experience that fields taken on patients, particularly neurosurgical patients, frequently do not follow exact textbook pictures in every detail but have to be smoothed out. This liberty has evidently been taken here, and from the viewpoint of pedagogy it is helpful.

Minor omissions and mistakes can be picked up in any book, but there are very few here. Only one merits mention, which is the arrangement of the fiber tracts in the chiasm. The generally accepted view that fibers entering the chiasm from the inferior nasal quadrant of each retina form the anterior loop in the opposite optic nerve and that fibers from each upper nasal quadrant form the posterior loop is not borne out by Figure 44. While this is a minor point, it tends to contradict clinical experience, in which the earliest field changes in pituitary tumors are upper temporal quadrant defects and the high incidence of loss of the entire temporal field on one side, combined with loss of the upper temporal quadrant on the opposite side.

Considerable praise should also be given to The C. V. Mosby Company for the beautiful printing and reproduction of the magnificient plates.

No ophthalmologist should be without this book.

Bone Structure and Metabolism: Ciba Foundation Symposium. Price, $6.75. Pp. 299. Little, Brown & Company, 34 Beacon St., Boston, 1956.

The subject of this symposium concerns the structure of bone from the anatomical to the molecular level, and anyone who has a problem in the physical or chemical structure of bone will probably find it thoroughly discussed by a group of experts in this book. It maintains the usual standard of excellence of all the Ciba Foundation symposia.

Paper Electrophoresis: Ciba Foundation Symposium. Price, $6.75. Pp. 224. Little, Brown & Company, 34 Beacon St., Boston, 1956.

This Ciba Foundation symposium was held in July, 1955. The subject is paper electrophoretic technique, which has become an increasingly important diagnostic tool. The general methods of paper electrophoresis and their use in medical problems are discussed by a group of experts.

Augenheilkunde. By Hugo Gasteiger. Ganzleinen DM 38 . Pp. 296. Walter de Gruyter & Co., Genthinerstrasse 13, Berlin W 35, 1956.

This book is intended primarily for the medical student and general practitioner. Various diseases of the eye are considered in anatomical order, beginning with the lids, and in addition there are chapters on injuries and refractive errors.

Written in German, it is well printed, with excellent illustrations.

Geometrical Optics. By L. C. Martin. Price, $7.50. Pp. 215, with 129 illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

This text is intended primarily for physicists and deals with geometrical optics from a mathematical point of view, although the author states that it demands "only a modest mathematical equipment in analytical geometry and elementary calculus." Until at least the calculus is required for those entering the study of ophthalmology, there will be few who will find this book readable.

At the end of each chapter are a series of exercises testing the student's comprehension of the text.

Dermatology. By Donald M. Pillsbury, M.D.; Walter B. Shelley, M.D., and Albert M. Kligman, M.D. Price, $20.00. Pp. 1331, with 564 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This authoritative work on dermatology will be of interest to ophthalmologists in treating patients with lesions of the skin of the lids. While there are no sections devoted specifically to lid conditions, the general principles of diagnosis and treatment are clearly described. Most dermatologic texts leave one confused by the ex cathedra diagnoses of rare skin lesions. In this book the authors have considerably simplified the diagnostic approach, and as a result it should now be possible for even an ophthalmologist to recognize and treat 90% of the conditions he sees in his office without recourse to further help.

The book is beautifully printed and illustrated.

L'Oedème papillaire: Rapport presente à la Société Française d'ophthalmologie. By Paul Brégeat. Masson & Cie, 120 Boulevard Saint-Germain, Paris, 6e, 1956.

This lengthy monograph is a compilation of information on edema of all causes gleaned from the literature of ophthalmology, neurology, neurosurgery, and internal medicine and from the experience of the author and his associates. The author brings together and classifies widely scattered material on papilledema, or, more precisely, edema of the optic nerve.

For the purpose of discussion, papilledema is classified either as secondary, in which some interference with the optic pathway is found, or as pure edema, in which no primary interference with the optic nerve fibers is found. This division is justified on the basis of clinical observation and eliminates the confusion and overlapping which result from consideration of the controversial problems of pathogenesis.

A preliminary section of the book reviews basic knowledge of the anatomy and physiology of the optic nerve. The physiopathology of edema, and in particular of edema of the nervous tissue, is discussed with special reference to physical and humoral agents active in its pathogenesis. Part two describes the clinical signs and symptoms of the two principal forms of papilledema. A section is devoted to the differentiation from false edema, or pseudoneuritis. The third part is concerned with an etiologic study of secondary edema, or optic neuritis, and with a classification of neurologic and non-neurologic causes of pure edema of the optic nerve.

The book is profusely illustrated and will serve as an excellent reference work for the ophthalmologist, neurologist, and neurosurgeon.

Textbook of Medical Physiology. By Arthur C. Guyton, M.D. Price, $13.50. Pp. 1030, with 577 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

It is remarkable to find in a textbook of physiology written for medical students an excellent account of the physiology of the eye, especially so since the whole book is from one pen. The author has devoted approximately 40 pages to a consideration of the function of the eye, and most of the material has been brought up to date and shows excellent judgment in its selection.

There are some statements for which the author would be hard put to find support. For example, he states that there is a reabsorption of protein from the aqueous into the capillaries of the iris as a result of some metabolic, enzymatic process at the surface of the iris. It is evident that this very unorthodox statement puzzled him, since he follows it by saying, "This is extremely important from a theorteical point of view, for active reabsorption of protein from any other tissues of the body is not known to occur."

The chapter on the retina is particularly well done, and this and the section on central nervous system ganglion and basic neuronal circuits should be read by every ophthalmologist interested in the applications of neurophysiological methods to ophthalmology.

Neurology of the Ocular Muscles. By David G. Cogan, M.D. Second edition. Price, $8.50. Pp. 296, with 85 illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1956.

The author prefaces the second edition of this valuable book by a general apology for all revisions and with some misgivings that he may disrupt the continuous and orderly presentation of his material by the additions and deletions. He need have no worry in this respect, for the very few criticisms which could be leveled at the previous edition seem to have been completely exenterated with skill, and the several changes in arrangement of the material have been most beneficial. Even if the second edition were no better and no worse than the first, the appearance of this volume on the shelf of many libraries throughout the country will be warmly welcomed, for it has long been out of print, and in many academic circles the one remaining copy has had to be kept under lock and key.

There are, in fact, not a great many changes in this book, and it remains a valuable text based on the author's extensive experience with alterations in ocular motility due to neuropathological conditions. If there is any criticism, it is of the author's penchant for adopting new terms, because the old ones are "confusing." The substitutions which he suggests are, in the opinion of the reviewer, worse than confusing. For example, he approves of the suggestion that disjunctive movements be called contraocular movements and that these "contraocular movements be abbreviated to "cont" movements. Thus, with the appropriate prefixes, we would have exo-cont, eso-cont, right- and left-hyper-cont, and eso-cyclo-cont and exo-cyclo-cont. Fortunately, it does not seem likely that these suggestions will be taken too seriously, except by their originator—guess who?

The book is some 80 pages longer than the first edition.

Lectures on Motor Anomalies. By A. Bielschowsky, with foreword by Walter Lancaster. Price, $2.50. Pp. 186, with 62 illustrations. Dartmouth Publications, Hanover, N. H., 1956.

The lectures which Alfred Bielschowsky delivered before the Research Study Club of Los Angeles in January, 1938, became a primer on motor anomalies for many of us at that time. They embodied the ideas of one who had spent his whole life in the study of disturbances of ocular motility and who had the facility to write in a lucid fashion on rather complex subjects. Most of Bielschowsky's ideas have been accepted and have been shown to be correct today, but the three different editions of his lectures have long

been exhausted, and the supply for residents has long since ceased to exist. It is extremely gratifying, therefore, that Dartmouth College has taken the initiative in reprinting these in the form of a monograph. No one who is interested in motor anomalies can afford not to read these lectures at some stage of his training.

Corneal Grafts. Edited by B. W. Rycroft, O.B.E., M.D., D.O.M.S., F.R.C.S. (Eng.). Price, $13.50. Pp. 285, with 155 black and white illustrations. Butterworth & Co., Ltd., 4-6 Bell Yard, Temple Bar, London, W. C. 2, 1956.

This text, edited by Rycroft, is composed of sixteen chapters written by fifteen ophthalmologists who have devoted much time and study to the problems of keratoplasty. The editor in assigning the chapters has selected for each author a topic of particular interest to that person. In this way he has succeeded in getting authoritative opinions on the various aspects of the subject. As with all volumes of multiple authorship, there is the unavoidable lack of continuity, but the material is presented in clear and concise terms. Among the chapters the reviewer found most interesting were those on anatomy and physiology of the cornea, the histopathology of corneal grafts, and lamellar keratoplasty. The indications for operation are too didactically stated for complete acceptance. The various operative techniques are fully described by surgeons of wide experience. To attest the completeness of this compact volume, one finds discussions on such topics as the use of contact lenses in corneal grafts, the preservation of the donor graft and donor material, and the law—all subjects of vital interest to the surgeon of the cornea. In the final chapter the editor gives a brief but interesting report on results. A most complete bibliography also enhances the value of this book. For the average ophthalmologist interested in the fundamentals of corneal grafting this volume can be highly recommended. Its low cost, small size, and readability are all desirable features lacking in some of the more comprehensive texts.

Comparative Anatomy of the Eye. By Jack H. Prince, M.D. Price, $8.50. Pp. 418. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1956.

A study of comparative anatomy in any field of medicine is valuable for the insight it affords the student of the evolution of structure in the human. This is particularly true in ophthalmology, where function is so closely related to structure. We have learned a great deal of the physiology of the human eye from comparative anatomy; for example, much of our knowledge of dark adaptation is supported by evidence derived from histological examination of various species of animals which have only one type of photoreceptor, i. e., rods or cones.

This book covers the same material treated in the well-known work of Walz on the vertebrate eye. In addition, there is a chapter on the invertebrate eye and a useful chapter on the preparation of specimens, a glossary of animal names used in the text, and a good bibliography. The material is arranged in anatomical sequence rather than from the point of view of orders or species of animals. The illustrations are excellent.

The author is an assistant research professor in the Department of Ophthalmology of The Ohio State University.

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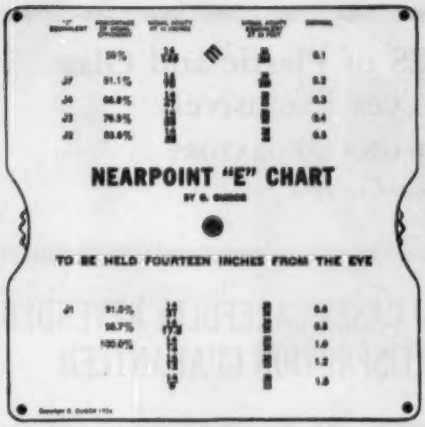

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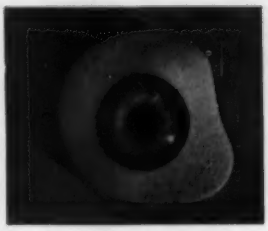

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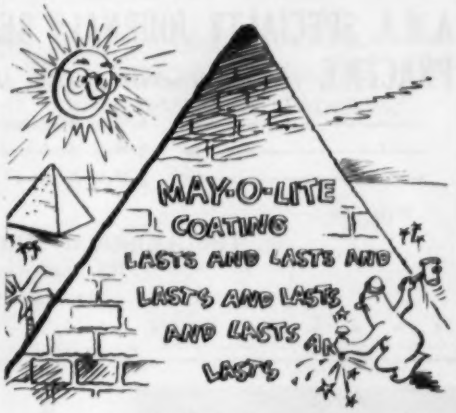

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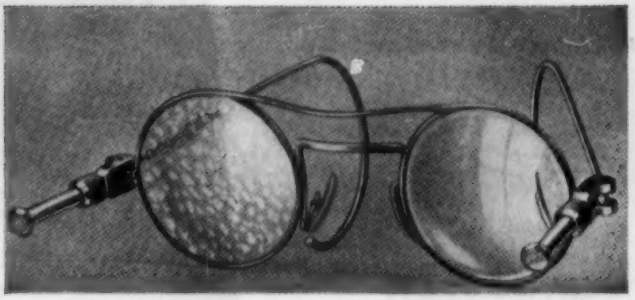

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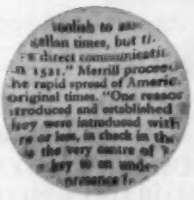

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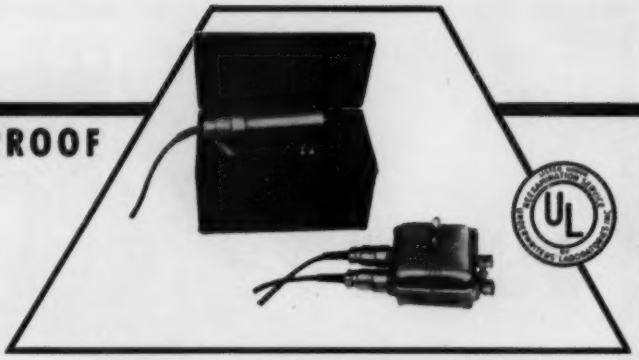

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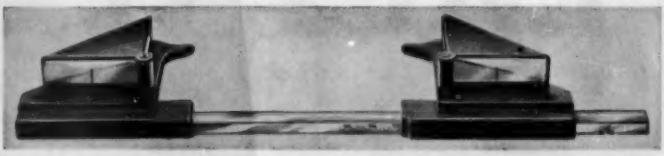

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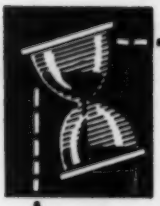

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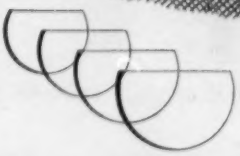

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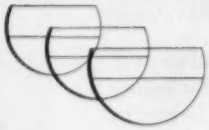

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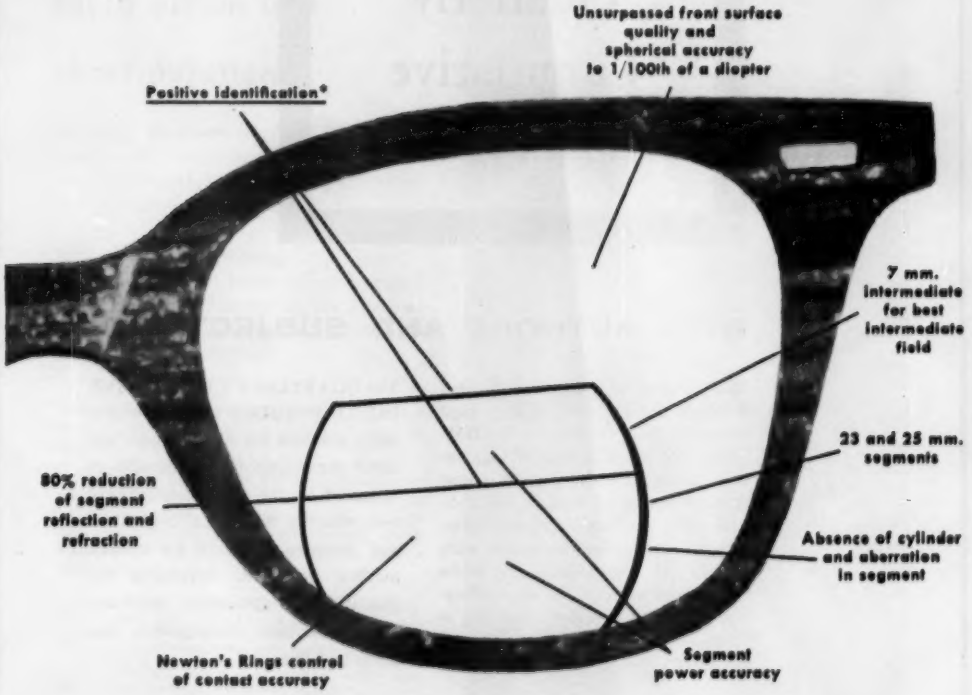
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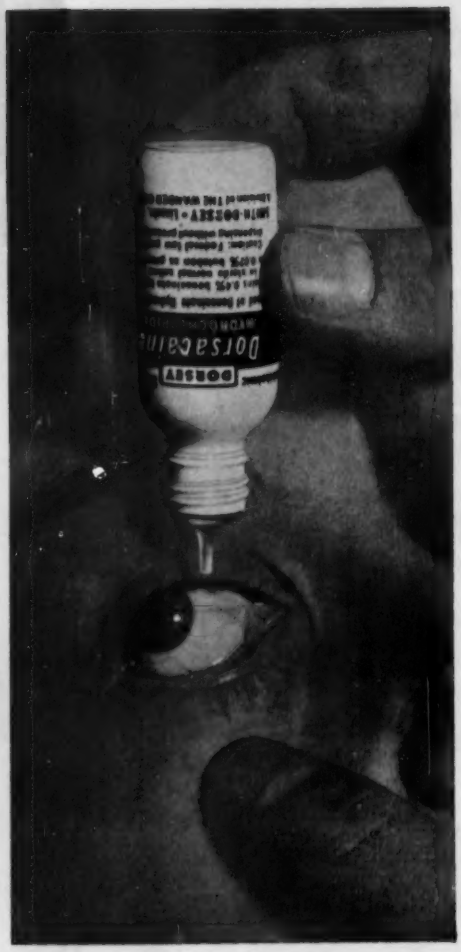

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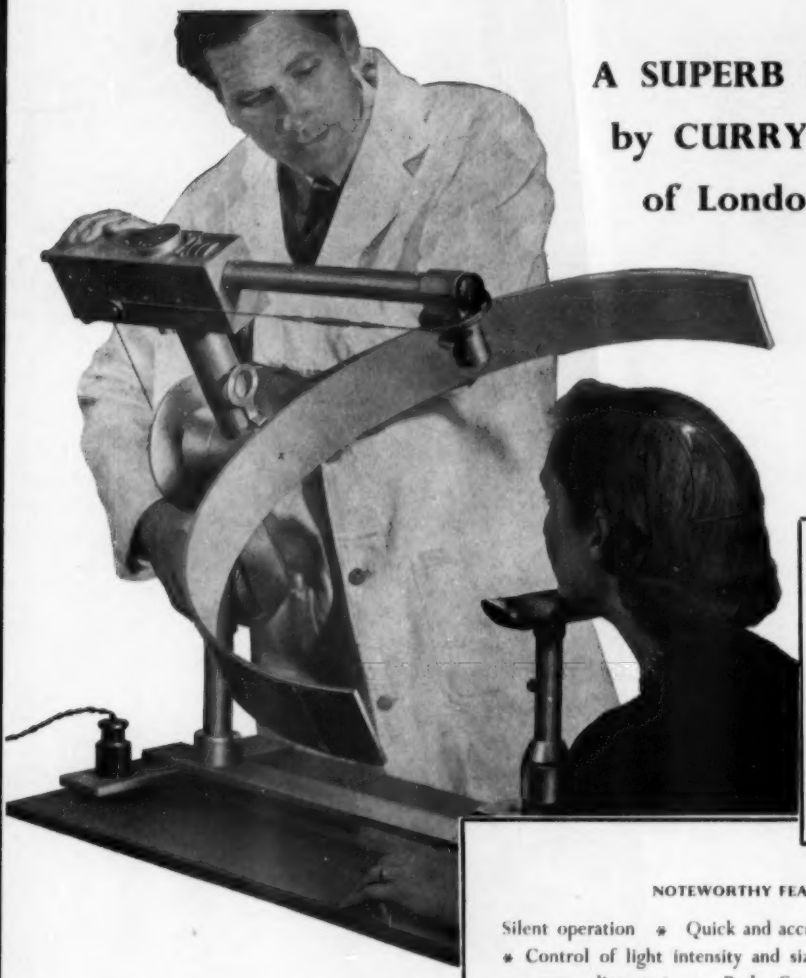

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